SEQUENCE LISTING

<110> The Trustees of the University of Pennsylvania
Stedman, Hansell
Su, Leonard
Mitchell, Marilyn

<120> Microutrophin and Uses Thereof

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<150> US 60/538,877
<151> 2004-01-23

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Gly Lys Pro Pro Ile Asn Asp Met Phe Thr Asp Leu Lys Asp Gly Arg
50 55 60

Lys Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Thr Ser Leu Pro Lys
65 70 75 80

Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
85 90 95

Leu Gln Val Leu His Gln Asn Asn Val Asp Leu Val Asn Ile Gly Gly
100 105 110

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Leu Trp
115 120 125

Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Val Met
130 135 140

Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
145 150 155 160

Arg Gln Ser Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
165 170 175

Thr Ser Trp Thr Asp Gly Leu Ala Phe Asn Ala Val Leu His Arg His
180 185 190

Lys Pro Asp Leu Phe Ser Trp Asp Arg Val Val Lys Met Ser Pro Ile
195 200 205

Glu Arg Leu Glu His Ala Phe Ser Lys Ala Gln Thr Tyr Leu Gly Ile
210 215 220

Glu Lys Leu Leu Asp Pro Glu Asp Val Ala Val Gln Leu Pro Asp Lys
225 230 235 240

Lys Ser Ile Ile Met Tyr Leu Thr Ser Leu Phe Glu Val Leu Pro Gln
245 250 255

Gln Val Thr Leu Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Gly Glu Ile Ser Ile Gln Ser Ser Ala
275 280 285

Pro Glu Glu Glu His Glu Cys Pro Gly Ala Glu Thr Pro Ser Thr Val
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Asp Ile Ser Asp Asp Val Glu Glu Val Lys Glu Gln Phe Thr Thr His
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Glu Ala Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
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Val Leu Gln Ala Gly Asn Gln Leu Ile Thr Gln Gly Thr Leu Ser Asp
370 375 380

Glu Glu Glu Phe Glu Ile Gln Glu Gln Met Thr Leu Leu Asn Ala Arg
385 390 395 400

Trp Glu Ala Leu Arg Val Asp Ser Met Asn Arg Gln Ser Arg Leu His
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Asp Val Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ala
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Trp Leu Thr Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Thr Cys Pro
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Arg Leu Gln Asn Asp Leu Glu Ala Glu Gln Val Lys Val Asn Ser Leu
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Thr His Met Val Val Ile Val Asp Glu Asn Ser Gly Glu Ser Ala Thr
485 490 495

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Val Cys Arg Trp Thr Glu Glu Arg Trp Ser Arg Leu Gln Glu Ile Asn
515 520 525

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Leu Thr Glu Lys Glu Glu Ala Leu Asn Lys Val Gln Thr Ser Asn Phe
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565 570 575

Lys Glu Asp Met Glu Met Lys Arg Gln Ala Leu Asp Gln Leu Ser Glu
580 585 590

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595 600 605

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625 630 635 640

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Arg Ile Arg Glu Gln Val Thr Thr Lys Arg Ser Lys Gln Glu Leu Pro
660 665 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile Pro Val Asp Leu Glu Lys

675 680 685

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690 695 700

Glu Ala Glu Ala Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
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725 730 735

Glu Ile Ala Pro Ile Asn Leu Lys Val Lys Thr Val Asn Asp Leu Ser
740 745 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
755 760 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val
770 775 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785 790 795 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
805 810 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
820 825 830

Thr Thr Cys Trp Asp Arg Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
835 840 845

Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Ile Lys
850 855 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Asn
865 870 875 880

Thr Thr Asn Glu Val Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
885 890 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
900 905 910

Gly Leu Glu Gln Met His Lys Asp Leu Val Asn Val Pro Leu Cys Val
915 920 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
930 935 940

Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
945 950 955 960

Lys Gly Leu Leu Glu Glu Lys Tyr Arg Tyr Leu Phe Lys Glu Val Ala
965 970 975

Gly Pro Thr Glu Met Cys Asp Gln Arg Gln Leu Gly Leu Leu Leu His
980 985 990

Asp Ala Ile Gln Ile Pro Arg Gln Leu Gly Glu Val Ala Ala Phe Gly
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Gly Ser Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Gln Asn
1010 1015 1020

Asn Asn Lys Pro Glu Ile Ser Val Lys Asp Phe Ile Asp Trp Met
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Arg Leu Glu Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg
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Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile
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Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser Leu Lys
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His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly Arg
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Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
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Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
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35 40 45

Asp Ile Gln Ala Glu Ile Asp Ala His Asn Asp Ile Phe Lys Ser Ile
50 55 60

Asp Gly Asn Arg Gln Lys Met Val Lys Ala Leu Gly Asn Ser Glu Glu
65 70 75 80

Ala Thr Met Leu Gln His Arg Leu Asp Asp Met Asn Gln Arg Trp Asn
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Asp Leu Lys Ala Lys Ser Ala Ser Ile Arg Ala His Leu Glu Ala Ser
100 105 110

Ala Glu Lys Trp Asn Arg Leu Leu Met Ser Leu Glu Glu Leu Ile Lys
115 120 125

Trp Leu Asn Met Lys Asp Glu Glu Leu Lys Lys Gln Met Pro Ile Gly
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Gly Asp Val Pro Ala Leu Gln Leu Gln Tyr Asp His Cys Lys Ala Leu
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Arg Arg Glu Leu Lys Glu Lys Glu Tyr Ser Val Leu Asn Ala Val Asp
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Gln Ala Arg Val Phe Leu Ala Asp Gln Pro Ile Glu Ala Pro Glu Glu
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195 200 205

Ala Gln Lys Ile Ala Lys Ala Met Arg Lys Gln Ser Ser Glu Val Lys
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Glu Lys Trp Glu Ser Leu Asn Ala Val Thr Ser Asn Trp Gln Lys Gln
225 230 235 240

Val Asp Lys Ala Leu Glu Lys Leu Arg Asp Leu Gln Gly Ala Met Asp

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Asp Leu Asp Ala Asp Met Lys Glu Ala Glu Ser Val Arg Asn Gly Trp
260 265 270

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275 280 285

Lys Ile Met Ala Phe Arg Glu Glu Ile Ala Pro Ile Asn Phe Lys Val
290 295 300

Lys Thr Val Asn Asp Leu Ser Ser Gln Leu Ser Pro Leu Asp Leu His
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Pro Ser Leu Lys Met Ser Arg Gln Leu Asp Asp Leu Asn Met Arg Trp
325 330 335

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340 345 350

Ala His Arg Asp Phe Gly Pro Ser Ser Gln His Phe Leu Ser Thr Ser
355 360 365

Val Gln Leu Pro Trp Gln Arg Ser Ile Ser His Asn Lys Val Pro Tyr
370 375 380

Tyr Ile Asn His Gln Thr Gln Thr Thr Cys Trp Asp His Pro Lys Met
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Thr Glu Leu Phe Gln Ser Leu Ala Asp Leu Asn Asn Val Arg Phe Ser
405 410 415

Ala Tyr Arg Thr Ala Ile Lys Ile Arg Arg Leu Gln Lys Ala Leu Cys
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Leu Asp Leu Leu Glu Leu Ser Thr Thr Asn Glu Ile Phe Lys Gln His
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Cys Leu Thr Thr Thr Tyr Asp Gly Leu Glu Gln Met His Lys Asp Leu
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Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn Trp Leu Leu Asn
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Val Tyr Asp Thr Gly Arg Thr Gly Lys Ile Arg Val Gln Ser Leu Lys
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Ile Gly Leu Met Ser Leu Ser Lys Gly Leu Leu Glu Glu Lys Tyr Arg
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Tyr Leu Phe Lys Glu Val Ala Gly Pro Thr Glu Met Cys Asp Gln Arg
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565 570 575

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Phe Ile Asp Trp Met His Leu Glu Pro Gln Ser Met Val Trp Leu Pro
595 600 605

Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys
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Arg Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys
660 665 670

Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val Leu
675 680 685

Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro Arg Leu
690 695 700

Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn Leu Glu Thr
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Pro Ile Thr Leu Ile Ser Met Trp Pro Glu His Tyr Asp Pro Ser Gln
725 730 735

Ser Pro Gln Leu Phe His Asp Asp Thr His Ser Arg Ile Glu Gln Tyr
740 745 750

Ala Thr Arg Leu Ala Gln Met Glu Arg Thr Asn Gly Ser Phe Leu Thr
755 760 765

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785                 790                 795                 800

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Glu Leu Glu Arg Ile Ile Ala Asp Leu Glu Glu Glu Gln Arg Asn Leu
            820                 825                 830

Gln Val Glu Tyr Glu Gln Leu Lys Asp Gln His Leu Arg Arg Gly Leu
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Pro Val Gly Ser Pro Pro Glu Ser Ile Ile Ser Pro His His Thr Ser
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Glu Asp Ser Glu Leu Ile Ala Glu Ala Lys Leu Leu Arg Gln His Lys
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Gly Arg Leu Glu Ala Arg Met Gln Ile Leu Glu Asp His Asn Lys Gln
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Leu Glu Ser Gln Leu His Arg Leu Arg Gln Leu Leu Glu Gln Pro Glu
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Ser Asp Ser Arg Ile Asn Gly Val Ser Pro Trp Ala Ser Pro Gln His
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Ser Ala Leu Ser Tyr Ser Leu Asp Pro Asp Ala Ser Gly Pro Gln Phe
    930                 935                 940

His Gln Ala Ala Gly Glu Asp Leu Leu Ala Pro Pro His Asp Thr Ser
945                 950                 955                 960

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35 40 45

Gly Lys Pro Pro Ile Asn Asp Met Phe Thr Asp Leu Lys Asp Gly Arg
50 55 60

Lys Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Thr Ser Leu Pro Lys
65 70 75 80

Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
85 90 95

Leu Gln Val Leu His Gln Asn Asn Val Glu Leu Val Asn Ile Gly Gly
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Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Leu Trp
115 120 125

Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Val Met
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Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Thr Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
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Lys Pro Asp Leu Phe Ser Trp Asp Lys Val Val Lys Met Ser Pro Ile
195 200 205

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Gln Val Thr Ile Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Glu Ala Ile Asn Ile Gln Ser Thr Ala
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Pro Glu Glu Glu His Glu Ser Pro Arg Ala Glu Thr Pro Ser Thr Val
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Thr Glu Val Asp Met Asp Leu Asp Ser Tyr Gln Ile Ala Leu Glu Glu
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Glu Ala Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
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385 390 395 400

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Asp Val Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ala
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Trp Leu Thr Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Thr Cys Pro
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Leu Asp Asp Asp Val Lys Ser Leu Gln Lys Leu Leu Glu Glu His Lys
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485 490 495

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Val Cys Arg Trp Thr Glu Glu Arg Trp Asn Arg Leu Gln Glu Ile Asn
515 520 525

Ile Leu Trp Gln Glu Leu Leu Glu Glu Gln Cys Leu Leu Lys Ala Trp
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Leu Thr Glu Lys Glu Glu Ala Leu Asn Lys Val Gln Thr Ser Asn Phe
545 550 555 560

Lys Asp Gln Lys Glu Leu Ser Val Ser Val Arg Arg Leu Ala Ile Leu
565 570 575

Lys Glu Asp Met Glu Met Lys Arg Gln Thr Leu Asp Gln Leu Ser Glu
580 585 590

Ile Gly Gln Asp Val Gly Gln Leu Leu Asp Asn Ser Lys Ala Ser Lys
595 600 605

Lys Ile Asn Ser Asp Ser Glu Glu Leu Thr Gln Arg Trp Asp Ser Leu
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Val Gln Arg Leu Glu Asp Ser Ser Asn Gln Val Thr Gln Ala Val Ala
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Lys Leu Gly Met Ser Gln Ile Pro Gln Lys Asp Leu Leu Glu Thr Val
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Arg Val Arg Glu Gln Ala Ile Thr Lys Lys Ser Lys Gln Glu Leu Pro
660 665 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile His Val Asp Leu Glu Lys
675 680 685

Leu Arg Asp Leu Gln Gly Ala Met Asp Asp Leu Asp Ala Asp Met Lys
690 695 700

Glu Ala Glu Ser Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
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Ile Asp Ser Leu Gln Asp His Ile Glu Lys Ile Met Ala Phe Arg Glu
725 730 735

Glu Ile Ala Pro Ile Asn Phe Lys Val Lys Thr Val Asn Asp Leu Ser
740 745 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
755 760 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val

770 775 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785 790 795 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
805 810 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
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Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
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850 855 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Ser
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Thr Thr Asn Glu Ile Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
885 890 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
900 905 910

Gly Leu Glu Gln Met His Lys Asp Leu Val Asn Val Pro Leu Cys Val
915 920 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
930 935 940

Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
945 950 955 960

Lys Gly Leu Leu Glu Glu Lys Tyr Arg Tyr Leu Phe Lys Glu Val Ala
965 970 975

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Gly Ser Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Gln Asn
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Asn Asn Lys Pro Glu Ile Ser Val Lys Glu Phe Ile Asp Trp Met
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His Leu Glu Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg
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Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile
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Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser Leu Lys
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His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly Arg
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Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys
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Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
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Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
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Gly Lys Pro Pro Ile Ser Asp Met Phe Ser Asp Leu Lys Asp Gly Arg
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Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
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Thr Asp Ile Val Ala Gly Asn Pro Lys Leu Thr Leu Gly Leu Leu Trp
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Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Ile Met
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Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Thr Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
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Thr Ser Trp Thr Asp Gly Leu Ala Phe Asn Ala Val Leu His Arg His
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Lys Pro Asp Leu Phe Asp Trp Asp Glu Met Val Lys Met Ser Pro Ile
195 200 205

Glu Arg Leu Asp His Ala Phe Asp Lys Ala His Thr Ser Leu Gly Ile
210 215 220

Glu Lys Leu Leu Ser Pro Glu Thr Val Ala Val His Leu Pro Asp Lys
225 230 235 240

Lys Ser Ile Ile Met Tyr Leu Thr Ser Leu Phe Glu Val Leu Pro Gln
245 250 255

Gln Val Thr Ile Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Glu Glu Ile His Ile Gln Ser Ala Val
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Thr Glu Val Asp Met Asp Leu Asp Ser Tyr Gln Ile Ala Leu Glu Glu
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Val Leu Thr Trp Leu Leu Ser Ala Glu Asp Thr Phe Gln Glu Gln His
325 330 335

Asp Ile Ser Asp Asp Val Glu Glu Val Lys Glu Gln Phe Ala Thr His
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Glu Thr Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
355 360 365

Val Leu Gln Ala Gly Asn Gln Leu Met Thr Gln Gly Thr Leu Ser Arg
370 375 380

Glu Glu Glu Phe Glu Ile Gln Glu Gln Met Thr Leu Leu Asn Ala Arg
385 390 395 400

Trp Glu Ala Leu Arg Val Glu Ser Met Glu Arg Gln Ser Arg Leu His
405 410 415

Asp Ala Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ser
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Trp Leu Ala Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Ser Leu Pro
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Leu Gly Asp Asp Leu Pro Ser Leu Gln Lys Leu Leu Gln Glu His Lys
450 455 460

Ser Leu Gln Asn Asp Leu Glu Ala Glu Gln Val Lys Val Asn Ser Leu
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Thr His Met Val Val Ile Val Asp Glu Asn Ser Gly Glu Ser Ala Thr
485 490 495

Ala Leu Leu Glu Asp Gln Leu Gln Lys Leu Gly Glu Arg Trp Thr Ala
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Val Cys Arg Trp Thr Glu Glu Arg Trp Asn Arg Leu Gln Glu Ile Ser
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Ile Leu Trp Gln Glu Leu Leu Glu Glu Gln Cys Leu Leu Glu Ala Trp
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Leu Thr Glu Lys Glu Glu Ala Leu Asp Lys Val Gln Thr Ser Asn Phe
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Lys Asp Gln Lys Glu Leu Ser Val Ser Val Arg Arg Leu Ala Ile Leu
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Lys Glu Asp Met Glu Met Lys Arg Gln Thr Leu Asp Gln Leu Ser Glu
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Ile Gly Gln Asp Val Gly Gln Leu Leu Ser Asn Pro Lys Ala Ser Lys
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Lys Met Asn Ser Asp Ser Glu Glu Leu Thr Gln Arg Trp Asp Ser Leu
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Val Gln Arg Leu Glu Asp Ser Ser Asn Gln Val Thr Gln Ala Val Ala
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Lys Leu Gly Met Ser Gln Ile Pro Gln Lys Asp Leu Leu Glu Thr Val
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His Val Arg Glu Gln Gly Met Val Lys Lys Pro Lys Gln Glu Leu Pro
660 665 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile His Val Asp Leu Glu Lys
675 680 685

Leu Arg Asp Leu Gln Gly Ala Met Asp Asp Leu Asp Ala Asp Met Lys
690 695 700

Glu Val Glu Ala Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
705 710 715 720

Ile Asp Ser Leu Gln Asp His Ile Glu Lys Thr Leu Ala Phe Arg Glu
725 730 735

Glu Ile Ala Pro Ile Asn Leu Lys Val Lys Thr Met Asn Asp Leu Ser
740 745 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
755 760 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val
770 775 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785 790 795 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
805 810 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
820 825 830

Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
835 840 845

Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Ile Lys
850 855 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Asn
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Thr Thr Asn Glu Val Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
885 890 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
900 905 910

Gly Leu Glu Gln Leu His Lys Asp Leu Val Asn Val Pro Leu Cys Val
915 920 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
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Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
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Lys Gly Leu Leu Glu Glu Lys Tyr Arg Cys Leu Phe Lys Glu Val Ala
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Gly Pro Thr Glu Met Cys Asp Gln Arg Gln Leu Gly Leu Leu Leu His
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Asp Ala Ile Gln Ile Pro Arg Gln Leu Gly Glu Val Ala Ala Phe Gly
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Gly Ser Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Gln Asn
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Asn Asn Lys Pro Glu Ile Ser Val Lys Glu Phe Ile Asp Trp Met
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His Leu Glu Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg
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Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile
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Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser Leu Lys
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His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly Arg
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Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys

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Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
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Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
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Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
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Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
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Leu Arg Val Leu Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser Thr
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Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp Asn
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Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met Ala
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Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val Arg
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Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr Thr
145 150 155 160

Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His Arg
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Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala Thr
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Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly Ile
195 200 205

Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp Lys
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Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro Gln
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Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg Pro
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Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met His
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Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg Thr
275 280 285

Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala Ala
290 295 300

Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln His
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Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu Ser
325 330 335

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Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile Ser
355 360 365

Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly Tyr
370 375 380

Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu Gln
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Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu Glu
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Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu Cys
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Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val Leu
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Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu Thr
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Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly Pro
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Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu Gln
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Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His Met
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Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala Leu
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Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ser Trp Leu Ser Glu
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Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp Gln
580 585 590

Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala Asp
595 600 605

Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys Gln
610 615 620

Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr Glu
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Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln Lys
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Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr Gln
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Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val Thr
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Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile Arg
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Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr Arg
725 730 735

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(21) International Application Number:
PCT/US2005/001768

(22) International Filing Date: 21 January 2005 (21.01.2005)

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(26) Publication Language: English

(30) Priority Data:
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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **STEDMAN, Hansell, H.** [US/US]; 1907 Berks Road, Norristown, PA 19403 (US). **SU, Leonard, T.** [US/US]; 1224 Heartwood Drive, Cherry Hill, NJ 08003 (US). **MITCHELL, Marilyn, A.** [US/US]; 4 University Mews, Philadelphia, PA 19104 (US).

(74) Agents: **KODROFF, Cathy** et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
27 April 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/118611 A3

(54) Title: MICROUTROPHIN AND USES THEREOF

(57) Abstract: A microutrophin containing a utrophin having internal deletions (relative to a native utrophin) in the hinge regions and a C-terminal deletion is provided. Also provided are vectors and compositions useful for delivering the microutrophin for the treatment of muscular disorders, including Duchenne Muscular Dystrophy.

INTERNATIONAL SEARCH REPORT

PCT/US05/01768

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 1/00, 14/00; C07H 21/02, 21/04; A61K 31/70
US CL : 530/350, 827; 536/23.1-23.5; 514/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/350, 827; 536/23.1-23.5; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
BioSci, Medicine, Caplus, Medline (in Dialog), PTO internal, Sequence databases-PTO internal and NPL: utrophin, dystrophin-related protein, dystrophin-like protein, DLP, DRP.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,518,413 B1 (TINSLEY et al.) 11 February 2003 (11.02.2003), Examples 1-2, column 12-17.	1,2,4,5,7-8 and 16-17
A	WO 01/25461 A1 (BURTON et al.) 12 April 2001 (12.04.2001), Abstract and claims 1-10.	7-8
A	GILBERT et al., Improved Performance of a Fully Gutted Adenovirus Vector Containing Two Full-Length Dystrophin cDNAs Regulated by a Strong Promoter. Molecular Therapy. October 2002. Vol. 6, No. 4, pp. 501-509. p. 502, 2nd column, 1st paragraph; pp. 502-503 and p. 507, 1st column, last two paragraphs.	1,2,4,5,7,8,16 and 17
L	VAN DEUTEKOM et al., Advances in Duchenne Muscular Dystrophy Gene Therapy. Nature Reviews Genetics. October 2003. Vol. 4, pp. 774-783. Figure 1. Shows Utrophin only has two hinge regions.	2
L	WINDER et al. Dystrophin and Utrophin: The Missing Link. FEBS Letters. 1995. Vol. 369, pp. 27-33. See p. 28, 1st column, 1st line.	2
A	BARANOV et al. The Current State and Prospects of the Gene Therapy of Duchenne Muscular Dystrophy Worldwide and in Russia. Russian Journal of Genetics. 2001. Col. 37, No. 8, pp. 868-875. Entire Document.	1,2, 4-8 and 16-17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
07 November 2005 (07.11.2005)

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/01768

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TINSLEY et al. Primary Structure of Dystrophin-Related Protein. Nature. December 1992. Vol. 360, pp.591-593. Entire Document.	1,2, 4-8 and 16-17
A	PERKINS et al. The Role Utrophin in the Potential Therapy of Duchenne Muscular Dystrophy. Neuromuscular Disorders. 2002. Vol. 12, pp. S78-S89. Entire Document.	1,2, 4-8 and 16-17
A	WILSON et al. Up71 and Up140, Two Novel Transcripts of Utrophin That Are Homologues of Short Forms of Dystrophin. Human Molecular Genetics. 1999. Vol. 8, No. 7, pp. 1271-1278. Entire document.	1,2, 4-8 and 16-17
A	AMANN et al. Utrophin Lacks the Rod Domain Actin Binding Domain of Dystrophin. The Journal of Biological Chemistry. December 1999. Vol. 274, No. 50, pp. 35375-35380. Entire Document.	1,2, 4-8 and 16-17
A	ATHENA et al., Cloning and Expression of Full Length Mouse Utrophin: The Differential Association of Utrophin and Dystrophin with AChR Clusters. FEBS Letters. 1996. Vol. 398, pp. 259-264. Entire Document.	1,2, 4-8 and 16-17
A	SQUIRE et al. Prevention of Pathology in mdx Mice by Expression of Utrophin: Analysis Using an Inducible Transgenic Expression System. Human Molecular Genetics. 2002. Vol. 11, No. 26, pp. 3333-3344. Entire Document.	1,2, 4-8 and 16-17

INTERNATIONAL SEARCH REPORT

PCT/US05/01768

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9-15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 9-15 were unsearchable as they are dependent upon 'any of claims 1-8; where there is no claim 3.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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(54) Title: MICROUTROPHIN AND USES THEREOF

(57) Abstract: A microutrophin containing a utrophin having internal deletions (relative to a native utrophin) in the hinge regions and a C-terminal deletion is provided. Also provided are vectors and compositions useful for delivering the microutrophin for the treatment of muscular disorders, including Duchenne Muscular Dystrophy.

MICROUTROPHIN AND USES THEREOF

STATEMENT OF FEDERALLY SPONSORED RESEARCH

The work described in this application was sponsored in part by a grant from the National Institutes of Health, grant number 5R01NS042874. The US government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

The present invention relates to the use of a microutrophin coding sequence in the treatment of muscular dystrophy.

Duchenne Muscular Dystrophy (DMD) is caused by a deficiency of the muscle cytoskeletal protein known as dystrophin. Dystrophin is a member of the spectrin superfamily of proteins and as such is distantly related to spectrin and alpha-actinin. Dystrophin is most closely related to the protein utrophin. The genes for these two proteins have nearly identical intron/exon structures, and the proteins are 50+% homologous at the amino acid level. Dystrophin is expressed throughout the entire length of the skeletal muscle fiber while utrophin is normally expressed only at the neuromuscular junction. Most cases of DMD result from sporadic deletions of the X chromosomal dystrophin gene. The destruction of the dystrophin open reading frame by these mutations suggests that therapies that genetically reconstitute dystrophin expression will elicit a cellular immune response against the fibers in which the protein is synthesized.

In the years following the initial discovery of utrophin, the technologies for targeted gene ablation in mice facilitated a formal genetic analysis of gene complementation. In the transgenic mouse in which the expression of utrophin is dictated by a muscle-specific promoter, utrophin can complement the physiological role of dystrophin.

Tinsley and Davies, US Patent No. 6,518,413, describe the expression of a polypeptide with utrophin function from a nucleic acid sequence for use in treatment of muscular dystrophy. This group designed a truncated protein modeled on a natural

mutation identified in a mild Becker muscular dystrophy patient. However, while the constructs provide some amelioration of symptoms, they are not optimal in terms of size, permissible delivery routes, or therapeutic outcome.

More recently, X. Xiao, US Patent Application Publn No. US 2003/0171312 A1 and J. Chamberlain, *et al*, US Patent Application Publn No. US 2003/0216332 A1, have described mini-dystrophin genes for use in treating muscular dystrophies. In the case of US 2003/0171312 A1, the dystrophin mini-gene may contain regions of the utrophin gene.

What is needed is an improved method of treating muscular dystrophies.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A to 1N provide the sequences of a canine microutrophin cDNA of the invention [nucleotides 12-3497 of SEQ ID NO:1] in alignment with a human microutrophin coding sequences of the invention [SEQ ID NO: 6] and a mouse microutrophin coding sequence of the invention [SEQ ID NO: 7].

Figs. 2A to 2E provide the sequences of a canine microutrophin of the invention [SEQ ID NO:2] in alignment with a human microutrophin of the invention [SEQ ID NO: 4] and a mouse microutrophin of the invention [SEQ ID NO: 5].

Fig. 3A to 2K provide an alignment of the human utrophin protein [SEQ ID NO:3] and the human dystrophin protein [SEQ ID NO: 8]. The repeats and hinge regions are marked with respect to the utrophin protein above the sequence and for the dystrophin protein below the sequence.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a vector comprising a microutrophin cassette useful in a medicament for treatment of muscular disorders, including muscular dystrophy.

In another aspect, the invention provides a pharmaceutical composition comprising the vector comprising the microutrophin cassette.

In yet another aspect, the invention provides a method of treating muscular dystrophies using microutrophin.

In still another aspect, the invention provides the use of a vector comprising a microutrophin cassette in the preparation of a medicament for treatment of muscular dystrophies.

Still other aspects and advantages of the invention will be apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides microutrophin useful in treatment of muscle wasting disorders characterized by dystrophic pathology and symptoms. The severe muscle wasting disorders include Duchenne muscular dystrophy (DMD) and the less debilitating Becker muscular dystrophy. The invention further provides pharmaceutical compositions, medicaments, and methods of use thereof, for treatment of such disorders.

Without wishing to be bound by theory, the inventors believe that the present invention is advantageous over prior dystrophin-based therapies, because such therapies are anticipated to cause an autoimmune response in subjects lacking the ability to express a functional native dystrophin gene. Further, the inventors believe that the present invention is advantageous over the previously described utrophin-based constructs of Tinsley and Davies, due to its design and the improved methods for delivery described herein.

The term "muscle cell" or "tissue" refers to a cell or group of cells derived from muscle, including but not limited to cells and tissue derived from skeletal muscle, cardiac muscle, smooth muscle, e.g., from the digestive tract, urinary bladder and blood vessels. The constructs of the invention can be delivered in vitro or in vivo, depending upon the application. Thus, for example, an isolated cardiomyocyte would constitute a "muscle cell" for purposes of the present invention, as would a muscle cell as it exists in muscle tissue present in a subject. The term also encompasses both differentiated and nondifferentiated muscle cells, such as myocytes, myotubes, myoblasts, cardiomyocytes and cardiomyoblasts, and progenitor cells, for example, the muscle derived stem cells or the bone marrow derived stem cells that can become muscle cells after differentiation.

The "microutrophin" of the invention is a utrophin polypeptide having a functional portion of the "actinin-binding domain" of about 270 amino acids relative to the human utrophin which is located within the N-terminal utrophin region, at least functional portions of the proline-rich hinge regions 1 and 4 (H1) and (H4), and a portion of the C-terminal utrophin protein. The microutrophin contains internal deletions in the central rod repeat domains and a truncation in the C-terminal region downstream, but retains the proper phasing (*i.e.*, conformation) to retain the desired biological function of utrophin. This construct of the invention is described in detail below.

Utrophin shows substantial homology to dystrophin, with significant divergence occurring in the rod domain, where utrophin lacks repeats 15 and 19 and two hinge regions (*See e.g.*, Love *et al.*, *Nature* **339**:55 [1989]; Winder *et al.*, *FEBS Lett.*, **369**:27 [1995]). Human utrophin contains 22 spectrin-like repeats and two hinge regions. *See, e.g.*, Genbank® accession number X69086 and GenBank® accession number AL357149, which provides full-length human UTRN gene for utrophin and encoded protein. Homologs of utrophin have been identified in a variety of organisms, including mouse (Genbank® accession number Y12229), rat (Genbank® accession number AJ002967), and dog (GenBank® accession number NW-139836). The nucleic acid sequence of these or additional homologs can be compared to the nucleic acid sequence of human utrophin using any suitable methods.

The "microutrophin" polypeptide provided in SEQ ID NO:2 and described in the examples is an artificial polypeptide containing an internal deletion and a C-terminal deletion, with respect to the native utrophin polypeptide. More particularly, the microutrophin polypeptide of Fig. 2 contains the N-terminal region of utrophin, hinge 1 (H1), and hinge 2 (H2), an internal deletion from Repeat 4 through Repeat 21, and, Repeat 22 through the C-terminal region until about Exon 63. The C-terminal region from Exon 63 through the native C-terminal region is deleted. Thus, the N-terminal utrophin amino acids through hinge 2 (H2) are fused to amino acids of Repeat 22 through the C-terminal region of Exon 62. The coding sequences for this polypeptide are provided in SEQ ID NO:1.

However, the microutrophin of the invention is not limited to this precise construct. Desirably, a microutrophin polypeptide contains amino acids from the N-terminal region of utrophin, at least two of the hinge regions, and all or a portion of the C-terminal region. In one embodiment, the N-terminal region of utrophin comprises a polypeptide from the N-terminus to about the hinge region (e.g., about amino acid 1 to 268 based on the aligned human utrophin sequence in Fig. 3 [SEQ ID NO:3].); however, shorter or longer fragments of the utrophin sequence N-terminal to the hinge region may be selected. For example, 1 to 10, 1 to 5, 2, 3 or 4 of the first amino acids of the N-terminal sequences may be deleted. In one embodiment, the microutrophin is deleted of all or a fragment of hinge region 3. In another embodiment, the microutrophin is deleted of a fragment of hinge region 4. Suitably, the deletions are selected such that they permit proper conformational alignment of the utrophin protein, and particularly, retain the critical triple helices formed by the utrophin polypeptide. Preferably, the C-terminal cysteine-rich (CR) domain is truncated from a location at about Exon 63 [about amino acid 3346 of SEQ ID NO: 3] through the end of the utrophin protein. In another embodiment, a longer portion of the C-terminal region, e.g., about Exon 64 – end, about Exon 65 – end, about Exon 66-end, or more, can be retained. In one embodiment, the microutrophin comprises the N-terminal region of utrophin, at least hinges H1 and hinge 4 (H4) of utrophin gene, and at least four of the central rod repeats of the utrophin genes.

Preferably, for use in human subjects, human microutrophin sequences are selected in order to minimize any immune response. Similarly, for a dog, canine sequences are preferably selected. The appropriate locations of the N-terminal, C-terminal, and internal deletions described herein in the context of the human and canine sequences can be readily determined for other utrophin homologs, by preparing an alignment and comparison to the sequences of human utrophin using any suitable methods.

The sequences encoding the microutrophin polypeptide, or the fragments thereof which are fused in frame to generate the microutropin, can be obtained by conventional techniques. For the experiments described herein, the utrophin sequences were obtained by reverse transcriptase (RT) polymerase chain reaction

(PCR) techniques from tissue from a dystrophic animal. Alternatively, utrophin sequences may be obtained from other suitable sources, or suitable fragments may be prepared using synthetic methods. The source of the microutrophin sequences is not a limitation of the present invention.

The term "microutrophin gene" or "microutrophin coding sequences" refers to a nucleic acid molecule containing sequences encoding the microutrophin constructs described herein. These sequences may be those encoding the native utrophin fragments for the constructed microutrophin polypeptide. Alternatively, the microutrophin gene may contain a modified N-terminal domain in which DNA sequences surrounding the original protein translation initiation codon ATG are modified. The N-terminus of the microutrophin gene may be modified to improve expression efficiency without affecting the functionality of the gene product. For example, the original sequence surrounding the translation initiation ATG codon of the utrophin gene may be substituted by the Kozak sequence to increase the efficiency of protein synthesis. In one embodiment of the current invention, the three nucleotides upstream of the coding sequence may be changed from "AAA" to "CCA" and the fourth nucleotide in the coding sequence may be changed from "C" to "G". The modified sequences are useful to enhance the yield and/or purification of microutrophin protein synthesis.

The nucleic acid sequences encoding microutrophin can be generated using techniques known to those of skill in the art and engineered into an appropriate expression cassette under the control of regulatory sequences which direct its expression in a cell. Suitably, the microutrophin expression cassette is inserted into a vector for targeting to a desired host cell and/or into a subject. The term "expression cassette" refers to a construct of genetic material that contains coding sequences and enough regulatory information to direct proper transcription and translation of the coding sequences in a recipient cell.

The microutrophin expression cassette may be introduced into a mammalian subject using a variety of methods. It may be delivered as a naked DNA with or without hydrodynamic-based or electroporation-based procedures. The microutrophin expression cassette can also be delivered using a suitable vector. A gene transfer

"vector" refers to any agent, such as a plasmid, phage, transposon, cosmid, chromosome, liposome, DNA-viral conjugates, RNA/DNA oligonucleotides, virus, bacteria, etc., which is capable of transferring gene sequences into cells. Thus, the term includes cloning and expression vehicles, as well as non-viral and viral vectors.

Non-viral vectors such as liposomes or virus-liposome complexes, or with viral vectors such as adenovirus, HSV, baculovirus, retrovirus, lentivirus, and preferably AAV. Expression of the microutrophin minigenes may be controlled by a number of regulatory elements, including but not limited to, AAV inverted terminal repeat (ITR), retrovirus long terminal repeat (LTR), cytomeglovirus (CMV) immediate early promoter and/or enhancer, CMV enhancer and chicken β-actin promoter (CB promoter), α-actin promoter, myosin promoter, muscle-specific creatine kinase (MCK) promoter and/or enhancer, and the like. In one embodiment, the muscle-specific promoters, including modified versions of the above promoters and the synthetic muscle promoters, may also be used.

Optionally, a vector is targeted to specific cells by linking a target molecule to the vector. A targeting molecule is any agent that is specific for a cell or tissue type of interest, including for example, a ligand, antibody, sugar, receptor, or other binding molecule. The invention is also intended to include such other forms of vectors which serve equivalent functions and which become known in the art subsequently hereto. The term "transduction" denotes the delivery of a DNA molecule to a recipient cell either *in vivo* or *in vitro*, via a replication-defective viral vector, such as via a recombinant AAV virion.

As used herein the term "regulatory sequences" pertains to sequences operably linked to the encoded gene product. In addition to the major elements identified above, the macromolecular complex (*e.g.*, a vector) also includes conventional control elements that are operably linked to the transgene in a manner that permits its transcription, translation and/or expression in a cell transfected with the macromolecular complex.

"Operably linked" refers to an arrangement of elements wherein the components so described are configured so as to perform their usual function. Thus, control elements operably linked to a coding sequence are capable of effecting the

expression of the coding sequence. The control elements need not be contiguous with the coding sequence, so long as they function to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between a promoter sequence and the coding sequence and the promoter sequence can still be considered "operably linked" to the coding sequence.

Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation (polyA) signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*i.e.*, Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance secretion of the encoded product. A great number of expression control sequences, including promoters that are native, constitutive, inducible and/or tissue-specific, are known in the art and may be utilized.

In one embodiment, the regulatory sequences are optimized for expression in the muscle and/or comprise tissue-specific promoters. For instance, if expression in skeletal muscle is desired, a promoter active in muscle can be used. These include the promoters from genes encoding skeletal β-actin, myosin light chain 2A, dystrophin, muscle creatine kinase, as well as synthetic muscle promoters with activities higher than naturally-occurring promoters (see Li *et al.*, *Nat. Biotech.*, **17**:241-245 (1999)). However, one of skill in the art can readily select a suitable constitutive, inducible, or regulated promoter.

Examples of constitutive promoters include, without limitation, the retroviral Rous sarcoma virus (RSV) LTR promoter (optionally with the RSV enhancer), the cytomegalovirus (CMV) promoter (optionally with the CMV enhancer) [see, *e.g.*, Boshart *et al*, *Cell*, **41**:521-530 (1985)], the SV40 promoter, the dihydrofolate reductase promoter, the β-actin promoter, the phosphoglycerol kinase (PGK) promoter, and the EF1 promoter [Invitrogen]. Inducible promoters allow regulation of gene expression and can be regulated by exogenously supplied compounds, environmental factors such as temperature, or the presence of a specific physiological state, *e.g.*, acute phase, a particular differentiation state of the cell, or in replicating cells only. Inducible promoters and inducible systems are available from a variety of

commercial sources, including, without limitation, Invitrogen, Clontech and Ariad. Many other systems have been described and can be readily selected by one of skill in the art. Examples of inducible promoters regulated by exogenously supplied compounds, include, the zinc-inducible sheep metallothionine (MT) promoter, the dexamethasone (Dex)-inducible mouse mammary tumor virus (MMTV) promoter, the T7 polymerase promoter system [International Patent Publication No. WO 98/10088]; the ecdysone insect promoter [No *et al*, *Proc. Natl. Acad. Sci. USA*, **93**:3346-3351 (1996)], the tetracycline-repressible system [Gossen *et al*, *Proc. Natl. Acad. Sci. USA*, **89**:5547-5551 (1992)], the tetracycline-inducible system [Gossen *et al*, *Science*, **268**:1766-1769 (1995), see also Harvey *et al*, *Curr. Opin. Chem. Biol.*, **2**:512-518 (1998)], the RU486-inducible system [Wang *et al*, *Nat. Biotech.*, **15**:239-243 (1997) and Wang *et al*, *Gene Ther.*, **4**:432-441 (1997)] and the rapamycin-inducible system [Magari *et al*, *J. Clin. Invest.*, **100**:2865-2872 (1997)]. Other types of inducible promoters that may be useful in this context are those that are regulated by a specific physiological state, *e.g.*, temperature, acute phase, a particular differentiation state of the cell, or in replicating cells only.

In another embodiment, the native promoter for the transgene will be used. The native promoter may be preferred when it is desired that expression of the transgene should mimic the native expression. The native promoter may be used when expression of the transgene must be regulated temporally or developmentally, or in a tissue-specific manner, or in response to specific transcriptional stimuli. In a further embodiment, other native expression control elements, such as enhancer elements, polyadenylation sites or Kozak consensus sequences may also be used to mimic the native expression.

Methods for assembling and producing a variety of different vectors defined herein are known to those of skill in the art and have been described in textbooks and in the literature. See, *e.g.*, Sambrook et al, Molecular cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY (2000). Production of the vector is not a limitation of the present invention.

An "AAV vector" refers to vectors derived from an adeno-associated virus serotype, including human AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, avian

AAV, ovian AAV, etc., AAV7 [International Patent Application No. PCT/US02/33629], AAV8 [International Patent Application No. PCT/US02/33629], human AAV9 [International Patent Application No. PCT/US04/028817], among others which have been described [G. Gao, *et al.*, *J Virol.* 2004 Jun;**78**(12):6381-8; G. Gao, *et al*, *Proc Natl Acad Sci U S A.* 2003 May 13;**100**(10):6081-6. Epub 2003 Apr 25], and to vectors derived from more than one AAV serotype (hybrid AAV vectors). For example, a hybrid AAV vector may contain DNA sequences derived from both AAV-1 and AAV-2. An AAV vector can have one or more of the AAV wild-type genes deleted in whole or part, preferably the rep and/or cap genes, but retain functional flanking ITR sequences. AAV vectors can be constructed using recombinant techniques that are known in the art to include one or more heterologous nucleotide sequences flanked on both ends (5' and 3') with functional AAV ITRs. In the practice of the invention, an AAV vector can include at least one AAV ITR and a suitable promoter sequence positioned upstream of the heterologous nucleotide sequence and at least one AAV ITR positioned downstream of the heterologous sequence.

A "recombinant AAV vector plasmid" refers to one type of recombinant AAV vector wherein the vector comprises a plasmid. As with AAV vectors in general, 5' and 3' ITRs flank the selected heterologous nucleotide sequence. AAV vectors can also include transcription sequences such as polyadenylation sites, as well as selectable markers or reporter genes, enhancer sequences, and other control elements which allow for the induction of transcription. Such control elements are described more fully below. In addition, an "AAV vector" can be stably introduced into a cell line or cell lines for the purpose of viral particle production. Such a cell line is usually termed as AAV packaging cell line.

As used herein, the term "recombinant AAV", "recombinant AAV particle" or "recombinant AAV virion" is defined as an infectious, replication-defective virus composed of an AAV protein shell encapsidating (i.e., surrounding with a protein coat) a heterologous nucleotide sequence, which in turn is flanked 5' and 3' by AAV ITRs. In this regard, single-stranded AAV nucleic acid molecules (either the sense/coding strand or the antisense/anticoding strand as those terms are generally

defined) can be packaged into an AAV virion; both the sense and the antisense strands are equally infectious. When the recombinant AAV DNA is equal to or smaller than 50% of the full length viral genome (about 5,000 nucleotides), it can also be packaged as double-stranded hairpin-like DNA into AAV virion. Such virion is also fully infectious.

The term "recombinant AAV particle" or "recombinant AAV virion" also refers to a hybrid AAV particle in which the AAV protein shell and the encapsulated nucleotide sequence may be derived from AAVs of different serotype. For example, a hybrid AAV particle may contain AAV-1 capsid proteins and AAV-2 ITRs, or vice versa. It is also possible to create hybrid AAV capsid proteins using coding sequences from two or more AAV capsid genes. In addition, the capsid protein of a recombinant AAV may be manipulated by mutation, deletion, and/or insertion of amino acid sequence in order to modify the tropism of the recombinant AAV (Wu *et al.* J. Virol **74**, 8635-47 [2000]; Girod *et al.* Nat Med **5**, 1052-1056 [1999]).

A number of techniques for constructing recombinant AAV are known in the art. See, *e.g.*, U.S. Pat. No. 5,173,414, Lebkowski *et al.* Mol Cell Biol **8**, 3988-3996 [1988]; Carter B J, Current Opinion in Biotechnology **3**, 533-539 [1992]; Muzyczka N, cited supra; and Zhou et al. J. Exp. Med. 179, 1867-1875 [1994]; Xiao *et al.* J. Virol. **72**, 2224-32 [1998]; also, International Patent Appln No. PCT/US02/33629], AAV8 [International Patent Appln No. PCT/US02/33629], human AAV9 [International Patent Appln No. PCT/US04/028817], among others which have been described [G. Gao, *et al.*, *J Virol.* 2004 Jun;**78**(12):6381-8; G. Gao, *et al*, *Proc Natl Acad Sci U S A*. 2003 May 13;**100**(10):6081-6. Epub 2003 Apr 25].

Other suitable vectors may be selected for targeting to a desired host cell including, *e.g.*, adenovirus, retroviral, lentivirus, and plasmids. Suitable methods for constructing adenoviral [e.g., S. Roy, *et al.*, Virology, 2004 Jul 1;**324**(2):361-72; WO 03/046124], lentiviral [*e.g.*, WO 01/83730; WO 99/61598; R. Zuffery *et al*, J. Virol., **72** (12):9873-9880 (Dec 1998); H. Miyoshi *et al*, J Virol, **72**(10):8150-8157 (Oct 1998) and plasmid vectors [see, *e.g.*, J. Sambrook, *et al*, "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor, NY (2000)] have been described.

Any of the above-described vectors carrying the microutrophin expression cassette may be formulated for delivery to host cells or a subject according to published methods. The vector is mixed with a physiologically compatible carrier for administration to a human or non-human mammalian patient. Suitable carriers may be readily selected by one of skill in the art in view of the route(s) of delivery. For example, one suitable carrier includes saline, which may be formulated with a variety of buffering solutions (e.g., phosphate buffered saline). Other exemplary carriers include sterile saline, lactose, sucrose, calcium phosphate, gelatin, dextran, agar, pectin, peanut oil, sesame oil, and water. The selection of the carrier is not a limitation of the present invention.

Optionally, the compositions of the invention may contain, in addition to the vector and carrier(s), other conventional pharmaceutical ingredients, such as preservatives, or chemical stabilizers. Suitable exemplary preservatives include chlorobutanol, potassium sorbate, sorbic acid, sulfur dioxide, propyl gallate, the parabens, ethyl vanillin, glycerin, phenol, and parachlorophenol. Suitable chemical stabilizers include gelatin and albumin.

The vectors are administered to a subject in an effective amount. By "subject" is meant any mammal, including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

As used herein, the term "effective amount" refers to a level which brings about at least partially a desired therapeutic or prophylactic effect in a tissue targeted by the method of the present invention. The infection with an effective amount of the vector carrying genetic material of interest can then result in the modification of the cellular activities, e.g., a change in phenotype, in a tissue targeted by the method of the present invention.

Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver or lung, orally, intranasally,

intratracheally, by inhalation, intravenously, intramuscularly, intraocularly, subcutaneously, intradermally, or by other routes of administration. Currently, intravenous and oral delivery routes are most desirable. However, other routes and combinations of different routes may be used, as desired.

Preferably, the constructs of the invention utilize promoters that direct expression in both skeletal and cardiac muscle. Such promoters may be constitutive promoters, examples of which are provided below. Alternatively, muscle specific promoters may be utilized. In one embodiment, the invention involves delivery of a microutrophin under the control of regulatory sequences comprising a promoter specific for skeletal muscle. In another embodiment, the invention involves delivery of a microutrophin under the control of regulatory sequences comprising a promoter specific for cardiac muscle. In still another embodiment, the invention involves delivery of a mixture of microutrophin vectors, one specifically targeting skeletal muscle and another specifically targeting cardiac muscle expression.

In one embodiment, delivery is accomplished by the global mycocardial perfusion method described in International Patent Application No. PCT/US2004/030463. In another embodiment, delivery is accomplished by the gene transfer methods described in International Patent Application No. PCT/US2004/031322, filed September 24, 2004. Briefly, this method involves transferring a microutrophin of the invention to muscle cells by exsanguinating a region of the subject's microvasculature and delivering the complex to this region under high hydrostatic pressure using a configuration of perfusion cannulae and balloon as required to protect heart and lung to protein the organs during perfusion. A balloon catheter having a balloon that extends substantially the full length of the aorta or vessel that is inserted into the subject is provided for use in the systemic delivery of vector. In still another embodiment, the invention provides for delivery via a perfusion circuit and surgical method is provided for delivering a substance to a subject's heart *in situ* during cardiopulmonary bypass surgery. The perfusion circuit defines a path for re-circulating a solution containing a macromolecular complex through a coronary circulation circuit through a subject's heart during a surgical

procedure in which the substance is prevented from being delivered to the subject's other organs. [US Patent Appln No. 60/614,892.]

Dosages of the vector will depend primarily on factors such as the condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective human dosage of the vector is generally in the range of from about 1 ml to about 100 ml of solution containing concentrations of from about 1×10^7 to 1×10^{16} genomes or particles vector. The dosage will be adjusted to balance the therapeutic benefit against any side effects and such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage resulting in vectors, preferably AAV vectors containing the minigene. Optionally, dosage regimens similar to those described for therapeutic purposes may be utilized for immunization using the compositions of the invention.

Optionally, therapy with microutrophin can be combined with other therapies.

Expression of the microutrophin minigene may be detected by immunofluorescent staining and immunoblotting (Western blotting). Microutrophin therapy may be monitored by measuring missing DAP complexes on the myofiber plasma membrane, including the sarcoglycan complex which is typically not found in untreated dystrophic muscle due to the primary deficiency of dystrophin. Alternatively, microutrophin therapy can be monitored by assessing that muscle is protected from pathological phenotypes.

In one aspect, the invention provides a kit for use by a clinician or other personnel. Typically, such a kit will contain a microutrophin vector of the invention and, optionally, instructions for reconstitution and/or delivery thereof. In another embodiment, the kit will contain the microutrophin vector in a physiologically compatible saline solution and, optionally, instructions for dilution, and performing a method as described herein.

The kit of the invention may also contain a balloon catheter to facilitate somatic gene transfer as described [International Patent Application No.

PCT/US2004/030463, or by the gene transfer methods described in International Patent Application No. PCT/US2004/031322, filed September 24, 2004], oxygen-transporting agent and/or at least one disposable element of an extracorporeal circulatory support and oxygenation system. For example, at least one disposable element can be an oxygenator having a hollow body, a liquid inlet in fluid communication with the interior of the body, a liquid outlet in fluid communication with the interior of the body, a gas inlet for providing gas to the interior of a gas chamber, at least one gas-permeable membrane separating the gas chamber from the interior of the body, and a gas outlet for permitting gas to exit from the gas chamber, whereby gas exchange is enabled between a fluid in the interior of the body and a gas in the gas chamber. The oxygenator may be constructed as described in US Patent No. 6,177,403, wherein the gas-permeable membrane comprises PTFE tubing extending within at least a portion of the tube, and wherein the gas chamber comprises the interior of the PTFE tubing.

The following examples are illustrative of the invention. However, it will be understood that the invention is not limited to the following specified embodiments, or the methods or techniques for production or expression described therein.

Example 1: Generation of Viral Vector containing Microutrophin Expression Cassette

To obtain the microutrophin, mRNA was extracted from frozen aliquot of canine muscle and reverse transcribed into cDNA using the RETROscript system (Ambion). The cDNA was used as template for PCR using primers for canine utrophin. The PCR products were analyzed on 1.2% agarose gel.

Two microutrophin fragments were made by PCR cloning using Taq polymerase (ROCHE) and canine cDNA as the template. The first fragment cDNA was amplified with the primers , 5' CCG CGG GTA CCA GGA TCC GTC GAC ATC GAT CCA CCA TGG CCA AGT ATG GAG AA (sense, SEQ ID NO: 9) and Hinge 2 (Sal), 5' GTC GAC AGG AAT CTG TCT CTT CTT TGG (antisense; SEQ ID NO: 10) . The second fragment used the primers, 3' Exon70 TTA AGG ATC

CTC GAG TTT TTC AAG TCT CTA AGT TGT CAC C, SEQ ID NO: 11; Rpt 24 (Sal) 5'-GTC GAC CTG GAG AAG CTC AGA GAC-3'; SEQ ID NO:12.

Two microutrophin fragments were then joined at a Sal I site to form the microutrophin cassette. PCR TOPO (Invitrogen) cloning vector according to manufacture's instruction.

The plasmid DNA was isolated and analyzed by restriction analysis to confirm the presence of the insert. The DNA was sequence to verify the presence of the gene. The microutrophin gene was isolated from the plasmid DNA (with ClaI and XhoI restriction sites) and cloned into an AAV vector plasmid containing a cytomegalovirus (CMV) promoter and the small poly (A) signal sequence to generate the viral vector AAV2/1-CMV microutrophin. The recombinant AAV serotype 2/1 was prepared by published methods [A. Auricchio et al, J Clin Invest. 110(40:499-504 (Aug 15 2002); W. Xiao et al, J Virol, 73:3994-4003 (1999); US Patent No. 6,759,237].

Example 2: Expression of Functional Microutrophin

The mdx mouse (Bulfield et al. Proc. Natl. Acad. Sci. USA 81, 1189-1192 [1984]) is an animal model of DMD [purchased from Jackson Laboratory]. The genetic lesion in the mdx dystrophin gene is a nonsense mutation at base 3185 of the mRNA that causes premature termination of translation within exon 23. This nonsense mutation precludes synthesis of a functional protein. The mdx mouse model was used to assess the histological and western blot appearance of recombinant canine microutrophin.

Briefly, AAV2/1-microutrophin was into the right quadricep muscle of the mdx mice (intramuscular injection) with $1x10^{12}$ GC particles of purified virus AAV microutrophin. Muscle samples were collected for examination at various time points (approximately 1 to 2 months) after vector injection.

Muscle cryosections were immunofluorescently stained with utrophin (N-terminus) mouse monoclonal antibody (Vector Labs) and donkey anti- mouse FITC (Jackson ImmunoResearch). Slides were examined with a Nikon microscope.

Protein expression was observed in the neuromuscular junctions and in low level staining of sarcolemma and vessel walls in mdx mice. Molecular weights are 133 kd for the microutrophin.

The construct will be further assessed in a German Short haired Pointer dog, because of its complete deletion of the dystrophin coding sequence (SJ Schatzberg, et al, Neuromuscul Disord. 1999 Jul;9(5):289-95.).

All documents and GenBank® citations identified herein are incorporated by reference. Numerous modifications to, and variations of, the specific embodiments described herein will be readily apparent to one of skill in the art. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS:

1. A nucleic acid molecule comprising nucleic acid sequence encoding microutrophin under the control of regulatory sequences which direct expression of the microutrophin in a host cell.

2. The nucleic acid molecule according to claim 1, wherein the microutrophin comprises an internal deletion of the native utrophin protein of hinge region 3.

4. The nucleic acid molecule according to claim 1, wherein the microutrophin comprises a C-terminal deletion from exon 63 through the C-terminal amino acid of the native utrophin protein.

5. The nucleic acid molecule according to claim 1, wherein the microutrophin comprises the N-terminal sequences of utrophin through at least two hinge regions, and a C-terminal region from repeat 22 through exon 63.

6. The nucleic acid molecule according to claim 1, wherein the microutrophin is selected from the group consisting of human microutrophin having the amino acid sequence of SEQ ID NO: 4. canine microutrophin having the amino acid sequence of SEQ ID NO:2, and mouse microutrophin having the amino acid sequence of SEQ ID NO:5.

7. The nucleic acid molecule according to claim 1, wherein the regulatory sequences comprise a constitutive promoter.

8. The nucleic acid molecule according to claim 1, wherein the regulatory sequences comprise a muscle-specific promoter.

9. A vector comprising the nucleic acid molecule of any of claims 1 to 8.

10. The vector according to claim 9, wherein said vector is selected from the group consisting of an adeno-associated viral vector and a plasmid vector.

11. A pharmaceutical composition comprising a vector according to claim 9 or 10 and a physiologically compatible carrier.

12. The pharmaceutical composition according to claim 11, wherein the carrier is a buffered saline solution.

13. Use of a nucleic acid molecule according to any of claims 1 – 8 in preparing a medicament.

14. Use according to claim 13 wherein the medicament is useful for treatment of muscular disorders.

15. Use according to claim 13 wherein the medicament is useful for treatment of Duchenne Muscular Dystrophy.

16. A method of treating dystrophin deficiency by delivery of a vector comprising a nucleic acid molecule according to claim 1 and a physiologically compatible carrier.

17. The method according to claim 16, wherein the vector is an adeno-associated viral vector.

FIG. 1A

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Mouse Microutro     1 ATGGCCAAGTATGGGGACCTTGAAGCCAGGCCTGATGATGGGCAGAACGA   50
Human Microutro     1 ATGGCCAAGTATGGAGAACATGAAGCCAGTCCTGACAATGGGCAGAACGA   50
Canine Microutr     1 ATGGCCAAGTATGGAGAACATGAAGCCAGTCCTGATAATGGGCAGAACGA   50
                      ************** ** * ********* *****  *************

Mouse Microutro    51 ATTCAGTGACATCATTAAGTCCAGATCTGATGAACACAATGATGTACAGA  100
Human Microutro    51 ATTCAGTGATATCATTAAGTCCAGATCTGATGAACACAATGACGTACAGA  100
Canine Microutr    51 ATTCAGTGACATCATTAAGTCCAGATCTGATGAACACAATGACGTGCAGA  100
                      ********* ******************************** ** ****

Mouse Microutro   101 AGAAAACCTTTACCAAATGGATAAACGCTCGATTTTCCAAGAGTGGGAAA  150
Human Microutro   101 AGAAAACCTTTACCAAATGGATAAATGCTCGATTTTCAAAGAGTGGGAAA  150
Canine Microutr   101 AGAAAACCTTTACCAAATGGATCAATGCGCGATTTTCAAAGAGTGGAAAA  150
                      ********************** ** ** ******** ******** ***

Mouse Microutro   151 CCACCCATCAGTGATATGTTCTCAGACCTCAAAGATGGGAGAAAGCTCTT  200
Human Microutro   151 CCACCCATCAATGATATGTTCACAGACCTCAAAGATGGAAGGAAGCTATT  200
Canine Microutr   151 CCACCCATCAATGATATGTTCACAGACCTCAAAGATGGAAGGAAGCTCCT  200
                      ********** ********** ********************* ** *****  *

Mouse Microutro   201 GGATCTTCTCGAAGGCCTCACAGGAACATCATTGCCAAAGGAACGTGGTT  250
Human Microutro   201 GGATCTTCTAGAAGGCCTCACAGGAACATCACTGCCAAAGGAACGTGGTT  250
Canine Microutr   201 GGATCTTCTGGAAGGCCTCACAGGAACATCACTGCCAAAGGAACGTGGTT  250
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FIG. 1B

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Mouse Microutro  251 CCACAAGGGTGCATGCCTTAAACAATGTCAACCGAGTGCTACAGGTTTTA  300
Human Microutro  251 CCACAAGGGTACATGCCTTAAATAACGTCAACAGAGTGCTGCAGGTTTTA  300
Canine Microutr  251 CCACAAGGGTACATGCTTTAAATAATGTCAACAGAGTGCTGCAGGTTTTG  300
                     ********** ***** ***** ** ****** ******* ********

Mouse Microutro  301 CATCAGAACAATGTGGACTTGGTGAATATTGGAGGCACGGACATTGTGGC  350
Human Microutro  301 CATCAGAACAATGTGGAATTAGTGAATATAGGGGGAACTGACATTGTGGA  350
Canine Microutr  301 CATCAGAATAATGTGGATTTAGTGAATATAGGAGGAACTGACATTGTAGA  350
                     ******** ******** ** ******** ** ** ** ******** *

Mouse Microutro  351 TGGAAATCCCAAGCTGACTTTAGGGTTACTCTGGAGCATCATTCTGCACT  400
Human Microutro  351 TGGAAATCACAAACTGACTTTGGGGTTACTTTGGAGCATCATTTTGCACT  400
Canine Microutr  351 TGGAAATCACAAACTGACTTTGGGATTACTTTGGAGCATCATTTTGCACT  400
                     ******** *** ******** ** ***** ************ ******

Mouse Microutro  401 GGCAGGTGAAGGATGTCATGAAAGATATCATGTCAGACCTGCAGCAGACA  450
Human Microutro  401 GGCAGGTGAAAGATGTCATGAAGGATGTCATGTCGGACCTGCAGCAGACG  450
Canine Microutr  401 GGCAGGTAAAAGATGTCATGAAAGATGTCATGTCAGACCTGCAGCAGACA  450
                     ******* ** *********** *** ******* **************

Mouse Microutro  451 AACAGCGAGAAGATCCTGCTGAGCTGGGTGCGGCAGACCACCAGGCCCTA  500
Human Microutro  451 AACAGTGAGAAGATCCTGCTCAGCTGGGTGCGTCAGACCACCAGGCCCTA  500
Canine Microutr  451 AACAGTGAGAAGATCCTACTGAGCTGGGTGCGCCAGTCTACTAGGCCGTA  500
                     ***** *********** ** *********** *** * ** ***** **
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FIG. 1C

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Mouse Microutro  501 CAGTCAAGTCAACGTCCTCAACTTCACCACCAGCTGGACCGATGGACTCG  550
Human Microutro  501 CAGCCAAGTCAACGTCCTCAACTTCACCACCAGCTGGACAGATGGACTCG  550
Canine Microutr  501 CAGCCAGGTCAACGTCCTCAACTTCACCACCAGCTGGACAGATGGACTGG  550
                     *** ** ********************************* ******** *

Mouse Microutro  551 CGTTCAACGCCGTGCTCCACCGGCACAAACCAGATCTCTTCGACTGGGAC  600
Human Microutro  551 CCTTTAATGCTGTCCTCCACCGACATAAACCTGATCTCTTCAGCTGGGAT  600
Canine Microutr  551 CCTTTAATGCTGTGCTGCACCGACATAAACCTGATCTCTTCAGCTGGGAT  600
                     * ** ** ** ** ** ***** ** ***** *********  ******

Mouse Microutro  601 GAGATGGTCAAAATGTCCCCAATTGAGAGACTTGACCATGCTTTTGACAA  650
Human Microutro  601 AAAGTTGTCAAAATGTCACCAATTGAGAGACTTGAACATGCCTTCAGCAA  650
Canine Microutr  601 AGAGTTGTCAAAATGTCCCCAATTGAGAGACTTGAACATGCCTTCAGCAA  650
                       * *********** ***************** ***** **   ***

Mouse Microutro  651 GGCCCACACTTCTTTGGGAATTGAAAAGCTCCTAAGTCCTGAAACTGTTG  700
Human Microutro  651 GGCTCAAACTTATTTGGGAATTGAAAAGCTGTTAGATCCTGAAGATGTTG  700
Canine Microutr  651 AGCTCAAACTTATTTGGGAATTGAAAAGCTGTTAGATCCTGAAGATGTTG  700
                      ** ** **** ******************  **  *******  *****

Mouse Microutro  701 CTGTGCATCTCCCTGACAAGAAATCCATAATTATGTATTTAACGTCTCTG  750
Human Microutro  701 CCGTTCGGCTTCCTGACAAGAAATCCATAATTATGTATTTAACATCTTTG  750
Canine Microutr  701 CCGTTCAACTTCCTGACAAGAAATCCATAATTATGTATTTAACATCTTTG  750
                     * ** *  ** ******************************** *** **
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FIG. 1D

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Mouse Microutro  751 TTTGAGGTGCTTCCTCAGCAAGTCACGATAGATGCCATCCGAGAGGTGGA  800
Human Microutro  751 TTTGAGGTGCTACCTCAGCAAGTCACCATAGACGCCATCCGTGAGGTAGA  800
Canine Microutr  751 TTTGAGGTGCTTCCTCAGCAAGTCACTCTAGATGCCATCCGTGAAGTAGA  800
                     ********** ********** **** ******** ** ** **

Mouse Microutro  801 GACTCTCCCAAGGAAGTATAAGAAAGAATGTGAAGAGGAAGAAATTCATA  850
Human Microutro  801 GACACTCCCAAGGAAATATAAAAAAGAATGTGAAGAAGAGGCAATTAATA  850
Canine Microutr  801 GACACTCCCAAGGAAATATAAGAAAGAATGTGAAGAAGGAGAGATTAGTA  850
                     *** ********** ***** ********** * * *** **

Mouse Microutro  851 TCCAGAGTGCAGTGCTGGCAGAGGAAGGCCAGAGTCCCCGAGCTGAGACC  900
Human Microutro  851 TACAGAGTACAGCGCCTGAGGAGGAGCATGAGAGTCCCCGAGCTGAAACT  900
Canine Microutr  851 TACAGAGCTCAGCGCCAGAGGAGGAGCATGAGTGTCCCGGAGCTGAAACC  900
                     * *****  *** **  *  *****     ** ***** ******* **

Mouse Microutro  901 CCTAGCACCGTCACTGAAGTGGACATGGATTTGGACAGCTACCAGATAGC  950
Human Microutro  901 CCCAGCACTGTCACTGAGGTCGACATGGATCTGGACAGCTATCAGATTGC  950
Canine Microutr  901 CCCAGCACTGTCACTGAAGTTGACACGGATCTGGACAGCTATCAGATAGC  950
                     ** ***** ******** ** **** **** ********** ***** **

Mouse Microutro  951 GCTAGAGGAAGTGCTGACGTGGCTGCTGTCCGCGGAGGACACGTTCCAGG 1000
Human Microutro  951 GTTGGAGGAAGTGCTGACCTGGTTGCTTTCTGCTGAGGACACTTTCCAGG 1000
Canine Microutr  951 ACTGGAGGAAGTGCTGACCTGGTTGCTTTCTGCCGAGGACACTTTCCAGG 1000
                       * ************** *** **** ** ** ******** *******
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FIG. 1E

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Mouse Microutro 1001 AGCAACATGACATTTCTGATGATGTCGAAGAAGTCAAAGAGCAGTTTGCT 1050
Human Microutro 1001 AGCAGGATGATATTTCTGATGATGTTGAAGAAGTCAAAGACCAGTTTGCA 1050
Canine Microutr 1001 AGCAGGATGACATTTCTGATGATGTAGAAGAAGTCAAAGAGCAGTTTACT 1050
                     ****  **** ********************** ****** *

Mouse Microutro 1051 ACCCATGAAACTTTTATGATGGAGCTGACAGCACACCAGAGCAGCGTGGG 1100
Human Microutro 1051 ACCCATGAAGCTTTTATGATGGAACTGACTGCACACCAGAGCAGTGTGGG 1100
Canine Microutr 1051 ACCCATGAAGCTTTTATGATGGAGCTGACAGCGCACCAGAGCAGTGTGGG 1100
                     ********* ************* ***** ** *********** *****

Mouse Microutro 1101 GAGCGTCCTGCAGGCTGGCAACCAGCTGATGACACAAGGGACTCTGTCCA 1150
Human Microutro 1101 CAGCGTCCTGCAGGCAGGCAACCAACTGATAACACAAGGAACTCTGTCAG 1150
Canine Microutr 1101 CAGTGTCCTGCAGGCAGGAAACCAGCTGATAACGCAAGGAACTCTGTCAG 1150
                      ** *********** ** ***** ***** ** ***** ********

Mouse Microutro 1151 GAGAGGAGGAGTTTGAGATCCAGGAACAGATGACCTTGCTGAATGCAAGG 1200
Human Microutro 1151 ACGAAGAAGAATTTGAGATTCAGGAACAGATGACCCTGCTGAATGCTAGA 1200
Canine Microutr 1151 ATGAGGAGGAATTTGAAATTCAGGAACAAATGACCCTGCTAAATGCTAGA 1200
                       ** ** ** ***** ** ******** ****** **** ***** **

Mouse Microutro 1201 TGGGAGGCGCTCCGGGTGGAGAGCATGGAGAGGCAGTCCCGGCTGCACGA 1250
Human Microutro 1201 TGGGAGGCTCTTAGGGTGGAGAGTATGGACAGACAGTCCCGGCTGCACGA 1250
Canine Microutr 1201 TGGGAGGCACTCAGGGTGGATAGTATGAACAGACAGTCCCGGCTGCATGA 1250
                     ******** **  ******* ** *** * ** ************** **
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FIG. 1F

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Mouse Microutro 1251 CGCTCTGATGGAGCTGCAGAAGAAACAGCTGCAGCAGCTCTCAAGCTGGC 1300
Human Microutro 1251 TGTGCTGATGGAACTGCAGAAGAAGCAACTGCAGCAGCTCTCCGCCTGGT 1300
Canine Microutr 1251 TGTGTTGATGGAACTACAAAAGAAGCAGTTGCAACAGCTCTCTGCCTGGT 1300
                      *   ******* ** ** ***** **  **** ********   ****

Mouse Microutro 1301 TGGCCCTCACAGAAGAGCGCATTCAGAAGATGGAGAGCCTCCCGCTGGGT 1350
Human Microutro 1301 TAACACTCACAGAGGAGCGCATTCAGAAGATGGAAACTTGCCCCCTGGAT 1350
Canine Microutr 1301 TAACACTCACAGAAGAACGCATTCAGAAGATGGAAACCTGCCCCCTGGAT 1350
                      *  * ******** ** ***************** *    *** **** *

Mouse Microutro 1351 GATGACCTGCCCTCCCTGCAGAAGCTGCTTCAAGAACATAAAAGTTTGCA 1400
Human Microutro 1351 GATGATGTAAAATCTCTACAAAAGCTGCTAGAAGAACATAAAAGTTTGCA 1400
Canine Microutr 1351 GATGATTTAAAATCCCTACAAAAGCTACTAGAAGATCATAAACGTTTGCA 1400
                      *****  *    ** ** ** ***** **  **** ****** *******

Mouse Microutro 1401 AAATGACCTTGAAGCTGAACAGGTGAAGGTAAATTCCTTAACTCACATGG 1450
Human Microutro 1401 AAGTGATCTTGAGGCTGAACAGGTGAAAGTAAATTCACTAACTCACATGG 1450
Canine Microutr 1401 AAATGATCTTGAGGCGGAACAGGTGAAGGTAAATTCACTAACACACATGG 1450
                      ** *** ***** ** ********** ********  **** *******

Mouse Microutro 1451 TGGTGATTGTGGATGAAAACAGTGGGGAGAGTGCCACAGCTCTTCTGGAA 1500
Human Microutro 1451 TGGTCATTGTTGATGAAAACAGTGGTGAGAGCGCTACAGCTATCCTAGAA 1500
Canine Microutr 1451 TGGTGATTGTTGATGAAAACAGTGGTGAGAGTGCCACTGCTGTTCTGGAA 1500
                      **** ***** ************** ***** ** ** *** * ** ***
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FIG. 1G

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Mouse Microutro 1501 GATCAGTTACAGAAACTGGGTGAGCGCTGGACAGCTGTATGCCGCTGGAC 1550
Human Microutro 1501 GACCAGTTACAGAAACTTGGTGAGCGCTGGACAGCAGTATGCCGTTGGAC 1550
Canine Microutr 1501 GATCAGTTACAGAAACTTGGTGAACGCTGGACAGCAGTGTGCCGTTGGAC 1550
                     ** ************** ***** ********** ** ***** *****

Mouse Microutro 1551 TGAAGAACGTTGGAACAGGTTGCAAGAAATCAGTATTCTGTGGCAGGAAT 1600
Human Microutro 1551 TGAAGAACGCTGGAATAGGTTACAAGAAATCAATATATTGTGGCAGGAAT 1600
Canine Microutr 1551 AGAGGAACGTTGGAGTAGGCTACAAGAAATTAATATATTGTGGCAGGAAT 1600
                      ** ***** ****  *** * ******** * ***  ************

Mouse Microutro 1601 TATTGGAAGAGCAGTGTCTGTTGGAGGCTTGGCTCACCGAAAAGGAAGAG 1650
Human Microutro 1601 TATTGGAAGAACAGTGCTTGTTGAAAGCTTGGTTAACCGAAAAAGAAGAG 1650
Canine Microutr 1601 TATTAGAAGAACAGTGCTTGTTGAAAGCTTGGCTAACTGAAAAAGAAGAG 1650
                     **** ***** *****  ***** * ****** * ** ***** ******

Mouse Microutro 1651 GCTTTGGATAAAGTTCAAACCAGCAACTTTAAAGACCAGAAGGAACTAAG 1700
Human Microutro 1651 GCTTTAAATAAAGTCCAGACAAGCAACTTCAAAGACCAAAAGGAACTAAG 1700
Canine Microutr 1651 GCCTTAAATAAAGTCCAGACGAGCAACTTCAAAGACCAAAAGGAACTAAG 1700
                     ** **  ******* ** ** ******** ******** ***********

Mouse Microutro 1701 TGTCAGTGTCCGGCGTCTGGCTATATTGAAGGAAGACATGGAAATGAAGA 1750
Human Microutro 1701 TGTCAGTGTTCGACGTCTGGCTATTTTGAAGGAAGACATGGAAATGAAGC 1750
Canine Microutr 1701 TGTCAGCATCCGACGATTGGCTATTTTGAAGGAAGACATGGAAATGAAAC 1750
                     ******  * ** **  ******* ************************
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FIG. 1H

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Mouse Microutro 1751 GGCAGACTCTGGATCAACTGAGTGAGATTGGCCAGGATGTGGGCCAATTA 1800
Human Microutro 1751 GTCAAACATTGGATCAGCTGAGTGAGATTGGCCAGGATGTGGGACAATTA 1800
Canine Microutr 1751 GTCAGGCATTGGATCAGCTGAGTGAGATTGGCCAGGATGTGGGCCAATTA 1800
                     * **  *  ******* ************************** ******

Mouse Microutro 1801 CTCAGTAATCCCAAGGCATCTAAGAAGATGAACAGTGACTCTGAGGAGCT 1850
Human Microutro 1801 CTTGATAATTCCAAGGCATCTAAGAAGATCAACAGTGACTCAGAGGAACT 1850
Canine Microutr 1801 GTTGATAATCCCAAGGCATCTAAGAAGATCAACAGTGACTCAGAGGAACT 1850
                      *   **** ******************** *********** ***** **

Mouse Microutro 1851 AACACAGAGATGGGATTCTCTGGTTCAGAGACTCGAAGACTCTTCTAACC 1900
Human Microutro 1851 GACTCAAAGATGGGATTCTTTGGTTCAGAGACTAGAAGATTCCTCCAACC 1900
Canine Microutr 1851 AACTCAGAGATGGGATTCTTTGGTTCAGAGACTAGAAGATTCCTCTAGCC 1900
                     ** ** ************ ************* ***** ** ** * **

Mouse Microutro 1901 AGGTGACTCAGGCGGTAGCGAAGCTCGGCATGTCCCAGATTCCACAGAAG 1950
Human Microutro 1901 AGGTGACTCAGGCTGTAGCAAAGCTGGGGATGTCTCAGATTCCTCAGAAG 1950
Canine Microutr 1901 AGGTGACTCAGGCTGTGGCAAAGCTGGGGATGTCCCAAATTCCTCAGAAA 1950
                     ************* ** ** ***** ** ***** ** ***** *****

Mouse Microutro 1951 GACCTATTGGAGACCGTTCATGTGAGAGAACAAGGGATGGTGAAGAAGCC 2000
Human Microutro 1951 GACCTTTTGGAGACTGTTCGTGTAAGAGAACAAGCAATTACAAAAAAATC 2000
Canine Microutr 1951 GATCTTCTGGAGACTGTTCGCATAAGAGAACAAGTAACTACAAAAAGGTC 2000
                     ** **  ******* ****   * **********  *     ** *   *
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FIG. 1I

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Mouse Microutro 2001 CAAGCAGGAACTGCCTCCTCCTCCCCCACCAAAGAAGAGACAGATTCACG 2050
Human Microutro 2001 TAAGCAGGAACTGCCTCCTCCTCCTCCCCCAAAGAAGAGACAGATCCATG 2050
Canine Microutr 2001 TAAGCAAGAACTGCCTCCTCCTCCTCCCCCAAAGAAGAGACAGATTCCTG 2050
                      ***** ***************** ** ***************** *  *

Mouse Microutro 2051 TGGACTTAGAGAAACTCCGAGACCTGCAGGGAGCTATGGACGACCTGGAC 2100
Human Microutro 2051 TGGATTTGGAGAAACTCAGAGACCTGCAGGGAGCTATGGATGACCTGGAC 2100
Canine Microutr 2051 TGGATCTGGAGAAGCTCAGAGACCTGCAGGGAGCCATGGATGACCTGGAT 2100
                      ****  * ***** *** ***************** ***** ********

Mouse Microutro 2101 GCAGACATGAAGGAGGTGGAGGCTGTGCGGAATGGCTGGAAGCCCGTGGG 2150
Human Microutro 2101 GCTGACATGAAGGAGGCAGAGTCCGTGCGGAATGGCTGGAAGCCCGTGGG 2150
Canine Microutr 2101 GTTGACATGAAGGAGGCGGAGGCTGTGAGGAATGGCTGGAAGCCTGTGGG 2150
                      *  *************  *** * *** ***************** *****

Mouse Microutro 2151 AGACCTGCTTATAGACTCCCTGCAGGATCACATCGAGAAAACCCTGGCGT 2200
Human Microutro 2151 AGACTTACTCATTGACTCGCTGCAGGATCACATTGAAAAAATCATGGCAT 2200
Canine Microutr 2151 AGACTTACTTATCGACTCACTGCAGGATCACATTGAAAAAACCATGGCAT 2200
                      **** * ** ** ***** ************** ** **** * **** *

Mouse Microutro 2201 TTAGAGAAGAAATTGCACCAATCAACTTAAAAGTAAAAACAATGAATGAC 2250
Human Microutro 2201 TTAGAGAAGAAATTGCACCAATCAACTTTAAAGTTAAAACGGTGAATGAT 2250
Canine Microutr 2201 TTAGAGAAGAAATTGCACCAATCAACCTAAAAGTTAAAACAGTGAATGAT 2250
                      ************************** * ***** *****  *******
```

FIG. 1J

```
Mouse Microutro 2251 CTGTCCAGTCAGCTGTCTCCACTTGACTTGCATCCATCTCTAAAGATGTC 2300
Human Microutro 2251 TTATCCAGTCAGCTGTCTCCACTTGACCTGCATCCCTCTCTAAAGATGTC 2300
Canine Microutr 2251 TTATCCAGTCAGCTGTCTCCACTTGACCTGCATCCATCTCTAAAGATGTC 2300
                      * ********************** ******* **************

Mouse Microutro 2301 TCGCCAGCTGGATGACCTTAATATGCGATGGAAACTTCTACAGGTTTCCG 2350
Human Microutro 2301 TCGCCAGCTAGATGACCTTAATATGCGATGGAAACTTTTACAGGTTTCTG 2350
Canine Microutr 2301 TCGCCAGCTAGATGACCTTAATATGCGATGGAAACTTCTGCAGGTTTCTG 2350
                     ********* *************************** * ******** *

Mouse Microutro 2351 TGGACGATCGCCTTAAGCAGCTCCAGGAAGCCCACAGAGATTTTGGGCCA 2400
Human Microutro 2351 TGGATGATCGCCTTAAACAGCTTCAGGAAGCCCACAGAGATTTTGGACCA 2400
Canine Microutr 2351 TGGATGATCGCCTTAAACAGCTTCAGGAAGCCCATAGAGATTTTGGGCCA 2400
                     **** *********** ***** *********** *********** ***

Mouse Microutro 2401 TCTTCTCAACACTTTCTGTCCACTTCAGTCCAGCTGCCGTGGCAGAGATC 2450
Human Microutro 2401 TCCTCTCAGCATTTTCTCTCTACGTCAGTCCAGCTGCCGTGGCAAAGATC 2450
Canine Microutr 2401 TCCTCTCAGCATTTTCTTTCTACTTCAGTCCAGCTGCCATGGCAAAGATC 2450
                     ** ***** ** ***** ** ** ************** ***** *****

Mouse Microutro 2451 CATTTCACATAATAAAGTGCCCTATTACATCAACCATCAAACACAGACAA 2500
Human Microutro 2451 CATTTCACATAATAAAGTGCCCTATTACATCAACCATCAAACACAGACCA 2500
Canine Microutr 2451 CATTTCACATAATAAAGTGCCCTATTACATCAACCATCAAACACAGACAA 2500
                     ********************************************** *
```

FIG. 1K

```
Mouse Microutro 2501 CCTGTTGGGATCATCCTAAAATGACTGAGCTCTTCCAATCCCTTGCTGAT 2550
Human Microutro 2501 CCTGTTGGGACCATCCTAAAATGACCGAACTCTTTCAATCCCTTGCTGAC 2550
Canine Microutr 2501 CTTGTTGGGACCGTCCTAAAATGACTGAACTCTTTCAATCTCTTGCTGAC 2550
                     * ******** * ************ ** ***** ***** ********

Mouse Microutro 2551 CTGAATAATGTACGTTTCTCTGCCTACCGCACAGCAATCAAAATTCGAAG 2600
Human Microutro 2551 CTGAATAATGTACGTTTTTCTGCCTACCGTACAGCAATCAAAATCCGAAG 2600
Canine Microutr 2551 CTGAATAATGTACGTTTCTCTGCCTACCGTACAGCCATCAAAATCCGAAG 2600
                     ***************** ********** ***** ******** *****

Mouse Microutro 2601 GCTGCAAAAAGCATTATGTCTGGATCTCTTAGAGCTGAATACGACGAATG 2650
Human Microutro 2601 ACTACAAAAAGCACTATGTTTGGATCTCTTAGAGTTGAGTACAACAAATG 2650
Canine Microutr 2601 ACTACAAAAAGCACTGTGTTTGGATCTCTTAGAGTTGAATACAACAAATG 2650
                      ** ********* * *** ************** *** *** ** ****

Mouse Microutro 2651 AAGTTTTCAAGCAGCACAAACTGAACCAAAATGATCAGCTCCTGAGTGTC 2700
Human Microutro 2651 AAATTTTCAAACAGCACAAGTTGAACCAAAATGACCAGCTCCTCAGTGTT 2700
Canine Microutr 2651 AAGTTTTCAAGCAGCACAAACTGAACCAAAATGATCAGCTTCTTAGCGTT 2700
                     ** ******* ********  ************* ***** ** ** **

Mouse Microutro 2701 CCAGACGTCATCAACTGTCTGACCACCACTTACGATGGGCTTGAGCAGCT 2750
Human Microutro 2701 CCAGATGTCATCAACTGTCTGACAACAACTTATGATGGACTTGAGCAAAT 2750
Canine Microutr 2701 CCAGATGTCATCAACTGTCTGACAACAACTTATGATGGTCTTGAACAAAT 2750
                     ***** ***************** ** ***** ***** ***** **  *
```

FIG. 1L

```
Mouse Microutro 2751 GCACAAGGACTTGGTCAATGTTCCACTCTGCGTCGATATGTGTCTCAACT 2800
Human Microutro 2751 GCATAAGGACCTGGTCAACGTTCCACTCTGTGTTGATATGTGTCTCAATT 2800
Canine Microutr 2751 GCATAAGGATCTGGTCAACGTTCCACTCTGTGTGGATATGTGTCTCAACT 2800
                     *** *****  ******* ********** ** ************** *

Mouse Microutro 2801 GGCTGCTCAACGTATACGACACGGGCCGGACTGGAAAAATTCGGGTACAG 2850
Human Microutro 2801 GGTTGCTCAATGTCTATGACACGGGTCGAACTGGAAAAATTAGAGTGCAG 2850
Canine Microutr 2801 GGTTGCTCAATGTGTATGACACGGGTCGAACTGGAAAAATAAGAGTGCAG 2850
                     ** ******* ** ** ******** ** ***********  * ** ***

Mouse Microutro 2851 AGTCTGAAGATTGGATTGATGTCTCTCTCCAAAGGCCTCTTAGAAGAGAA 2900
Human Microutro 2851 AGTCTGAAGATTGGATTAATGTCTCTCTCCAAAGGTCTCTTGGAAGAAAA 2900
Canine Microutr 2851 AGTCTGAAGATTGGATTGATGTCTCTCTCCAAAGGTCTCTTAGAAGAAAA 2900
                     ***************** ***************** ***** ***** **

Mouse Microutro 2901 ATACAGATGTCTCTTTAAGGAGGTGGCAGGGCCAACTGAGATGTGTGACC 2950
Human Microutro 2901 ATACAGATATCTCTTTAAGGAAGTTGCGGGGCCGACAGAAATGTGTGACC 2950
Canine Microutr 2901 ATACAGATATCTCTTTAAGGAGGTGGCAGGTCCGACAGAAATGTGTGACC 2950
                     ******** ************ ** ** ** ** ** ** **********

Mouse Microutro 2951 AGCGGCAGCTTGGCCTGCTACTTCACGATGCCATCCAGATCCCTAGGCAG 3000
Human Microutro 2951 AGAGGCAGCTGGGCCTGTTACTTCATGATGCCATCCAGATCCCCCGGCAG 3000
Canine Microutr 2951 AGAGGCAGCTTGGCCTGTTACTTCATGATGCCATCCAGATCCCTCGGCAG 3000
                     ** ******* ****** ******* *****************  *****
```

FIG. 1M

```
Mouse Microutro 3001 CTGGGGGAAGTAGCAGCCTTTGGGGGCAGTAACATTGAGCCCAGTGTCCG 3050
Human Microutro 3001 CTAGGTGAAGTAGCAGCTTTTGGAGGCAGTAATATTGAGCCTAGTGTTCG 3050
Canine Microutr 3001 CTGGGGGAAGTAGCAGCTTTTGGGGGCAGTAATATTGAACCCAGTGTTCG 3050
                     ** ** ********** ***** ******** ***** ** ***** **

Mouse Microutro 3051 CAGCTGCTTCCAGCAGAATAACAACAAGCCAGAAATCAGTGTGAAGGAGT 3100
Human Microutro 3051 CAGCTGCTTCCAACAGAATAACAATAAACCAGAAATAAGTGTGAAAGAGT 3100
Canine Microutr 3051 CAGCTGCTTCCAACAGAATAACAATAAGCCAGAGATAAGCGTAAAAGATT 3100
                     ************ *********** ** ***** ** ** ** ** ** *

Mouse Microutro 3101 TTATAGACTGGATGCATTTGGAACCCCAGTCCATGGTGTGGTTGCCGGTT 3150
Human Microutro 3101 TTATAGATTGGATGCATTTGGAACCACAGTCCATGGTTTGGCTCCCAGTT 3150
Canine Microutr 3101 TTATAGATTGGATGCGTCTGGAACCACAGTCCATGGTTTGGCTGCCAGTT 3150
                     ******* ******* * ******* *********** *** * ** ***

Mouse Microutro 3151 CTGCATCGGGTCGCAGCTGCTGAGACTGCAAAACATCAGGCCAAATGCAA 3200
Human Microutro 3151 TTACATCGAGTGGCAGCAGCGGAGACTGCAAAACATCAGGCCAAATGCAA 3200
Canine Microutr 3151 TTACACCGAGTGGCTGCAGCTGAGACTGCAAAGCATCAAGCTAAATGCAA 3200
                      * ** ** ** ** ** ** ********** ***** ** ********

Mouse Microutro 3201 CATCTGCAAAGAATGCCCGATTGTTGGGTTCAGATACAGGAGCCTAAAGC 3250
Human Microutro 3201 CATCTGTAAAGAATGTCCAATTGTCGGGTTCAGGTATAGAAGCCTTAAGC 3250
Canine Microutr 3201 CATCTGTAAAGAATGTCCAATAGTTGGGTTCAGGTATAGAAGCCTAAAGC 3250
                     ****** ******** ** ** ** ******** ** ** ***** ****
```

FIG. 1N

```
Mouse Microutro 3251 ATTTTAATTATGATGTCTGCCAGAGTTGCTTCTTTTCTGGAAGAACAGCA 3300
Human Microutro 3251 ATTTTAACTATGATGTCTGCCAGAGTTGTTTCTTTTCGGGTCGAACAGCA 3300
Canine Microutr 3251 ATTTTAACTATGATGTCTGCCAGAGTTGCTTTTTTTCGGGTCGAACGGCA 3300
                     ******* ******************** ** ***** **  **** ***

Mouse Microutro 3301 AAGGGCCACAAGTTACATTACCCGATGGTAGAATACTGCATACCGACAAC 3350
Human Microutro 3301 AAAGGTCACAAATTACATTACCCAATGGTGGAATATTGTATACCTACAAC 3350
Canine Microutr 3301 AAAGGTCACAAATTACATTACCCAATGGTGGAATATTGTATACCTACAAC 3350
                     ** ** ***** ********** ***** ***** ** ***** *****

Mouse Microutro 3351 ATCTGGGGAAGATGTGAGAGATTTCACTAAGGTGCTGAAGAACAAGTTCA 3400
Human Microutro 3351 ATCTGGGGAAGATGTACGAGACTTCACAAAGGTACTTAAGAACAAGTTCA 3400
Canine Microutr 3351 ATCTGGGGAAGATGTACGAGACTTCACAAAGGTGCTGAAGAATAAGTTCA 3400
                     **************  **** ***** ***** ** ***** *******

Mouse Microutro 3401 GGTCCAAGAAATATTTTGCCAAACATCCTCGGCTTGGCTACCTGCCTGTC 3450
Human Microutro 3401 GGTCGAAGAAGTACTTTGCCAAACACCCTCGACTTGGTTACCTGCCTGTC 3450
Canine Microutr 3401 GATCAAAGAAATACTTTGCCAAACATCCTCGGCTTGGCTACCTGCCTGTC 3450
                     * ** ***** ** ********** ***** ***** ************

Mouse Microutro 3451 CAGACCGTGCTGGAAGGGGACAACTTAGAAACTTGA 3486
Human Microutro 3451 CAGACAGTTCTTGAAGGTGACAACTTAGAGACTTGA 3486
Canine Microutr 3451 CAGACAGTACTTGAAGGTGACAACTTAGAGACTTGA 3486
                     ***** ** ** ***** ********** ******
```

FIG. 2A

```
Canine Microutr     1 MAKYGEHEASPDNGQNEFSDIIKSRSDEHNDVQKKTFTKWINARFSKSGK   50
Human Microutro     1 MAKYGEHEASPDNGQNEFSDIIKSRSDEHNDVQKKTFTKWINARFSKSGK   50
Mouse Microutro     1 MAKYGDLEARPDDGQNEFSDIIKSRSDEHNDVQKKTFTKWINARFSKSGK   50
                      *****. ** ** ************************************

Canine Microutr    51 PPINDMFTDLKDGRKLLDLLEGLTGTSLPKERGSTRVHALNNVNRVLQVL  100
Human Microutro    51 PPINDMFTDLKDGRKLLDLLEGLTGTSLPKERGSTRVHALNNVNRVLQVL  100
Mouse Microutro    51 PPISDMFSDLKDGRKLLDLLEGLTGTSLPKERGSTRVHALNNVNRVLQVL  100
                      *** ***.****************************************

Canine Microutr   101 HQNNVDLVNIGGTDIVDGNHKLTLGLLWSIILHWQVKDVMKDVMSDLQQT  150
Human Microutro   101 HQNNVELVNIGGTDIVDGNHKLTLGLLWSIILHWQVKDVMKDVMSDLQQT  150
Mouse Microutro   101 HQNNVDLVNIGGTDIVAGNPKLTLGLLWSIILHWQVKDVMKDIMSDLQQT  150
                      *****.********** ** **********************.*******

Canine Microutr   151 NSEKILLSWVRQSTRPYSQVNVLNFTTSWTDGLAFNAVLHRHKPDLFSWD  200
Human Microutro   151 NSEKILLSWVRQTTRPYSQVNVLNFTTSWTDGLAFNAVLHRHKPDLFSWD  200
Mouse Microutro   151 NSEKILLSWVRQTTRPYSQVNVLNFTTSWTDGLAFNAVLHRHKPDLFDWD  200
                      ************.********************************** **

Canine Microutr   201 RVVKMSPIERLEHAFSKAQTYLGIEKLLDPEDVAVQLPDKKSIIMYLTSL  250
Human Microutro   201 KVVKMSPIERLEHAFSKAQTYLGIEKLLDPEDVAVRLPDKKSIIMYLTSL  250
Mouse Microutro   201 EMVKMSPIERLDHAFDKAHTSLGIEKLLSPETVAVHLPDKKSIIMYLTSL  250
                       .*********.*** **.* ******* ** ***.**************
```

FIG. 2B

```
Canine Microutr  251 FEVLPQQVTLDAIREVETLPRKYKKECEEGEISIQSSAPEEEHECPGAET  300
Human Microutro  251 FEVLPQQVTIDAIREVETLPRKYKKECEEEAINIQSTAPEEEHESPRAET  300
Mouse Microutro  251 FEVLPQQVTIDAIREVETLPRKYKKECEEEEIHIQSAVLAEEGQSPRAET  300
                     *********.******************  * ***.   ** ..* ***

Canine Microutr  301 PSTVTEVDTDLDSYQIALEEVLTWLLSAEDTFQEQDDISDDVEEVKEQFT  350
Human Microutro  301 PSTVTEVDMDLDSYQIALEEVLTWLLSAEDTFQEQDDISDDVEEVKDQFA  350
Mouse Microutro  301 PSTVTEVDMDLDSYQIALEEVLTWLLSAEDTFQEQHDISDDVEEVKEQFA  350
                     ******** ************************ **********.**.

Canine Microutr  351 THEAFMMELTAHQSSVGSVLQAGNQLITQGTLSDEEEFEIQEQMTLLNAR  400
Human Microutro  351 THEAFMMELTAHQSSVGSVLQAGNQLITQGTLSDEEEFEIQEQMTLLNAR  400
Mouse Microutro  351 THETFMMELTAHQSSVGSVLQAGNQLMTQGTLSREEEFEIQEQMTLLNAR  400
                     ***.**********************.****** ****************

Canine Microutr  401 WEALRVDSMNRQSRLHDVLMELQKKQLQQLSAWLTLTEERIQKMETCPLD  450
Human Microutro  401 WEALRVESMDRQSRLHDVLMELQKKQLQQLSAWLTLTEERIQKMETCPLD  450
Mouse Microutro  401 WEALRVESMERQSRLHDALMELQKKQLQQLSSWLALTEERIQKMESLPLG  450
                     ******.** ******* *************.**.**********. **

Canine Microutr  451 DDLKSLQKLLEDHKRLQNDLEAEQVKVNSLTHMVVIVDENSGESATAVLE  500
Human Microutro  451 DDVKSLQKLLEEHKSLQSDLEAEQVKVNSLTHMVVIVDENSGESATAILE  500
Mouse Microutro  451 DDLPSLQKLLQEHKSLQNDLEAEQVKVNSLTHMVVIVDENSGESATALLE  500
                     **. ******..** ** ****************************.**

Canine Microutr  501 DQLQKLGERWTAVCRWTEERWSRLQEINILWQELLEEQCLLKAWLTEKEE  550
Human Microutro  501 DQLQKLGERWTAVCRWTEERWNRLQEINILWQELLEEQCLLKAWLTEKEE  550
Mouse Microutro  501 DQLQKLGERWTAVCRWTEERWNRLQEISILWQELLEEQCLLEAWLTEKEE  550
                     ********************* ***** ************* ********
```

FIG. 2C

```
Canine Microutr  551 ALNKVQTSNFKDQKELSVSIRRLAILKEDMEMKRQALDQLSEIGQDVGQL  600
Human Microutro  551 ALNKVQTSNFKDQKELSVSVRRLAILKEDMEMKRQTLDQLSEIGQDVGQL  600
Mouse Microutro  551 ALDKVQTSNFKDQKELSVSVRRLAILKEDMEMKRQTLDQLSEIGQDVGQL  600
                     ** ***************.***************.**************  .

Canine Microutr  601 VDNPKASKKINSDSEELTQRWDSLVQRLEDSSSQVTQAVAKLGMSQIPQK  650
Human Microutro  601 LDNSKASKKINSDSEELTQRWDSLVQRLEDSSNQVTQAVAKLGMSQIPQK  650
Mouse Microutro  601 LSNPKASKKMNSDSEELTQRWDSLVQRLEDSSNQVTQAVAKLGMSQIPQK  650
                       . * *****.********************** *****************

Canine Microutr  651 DLLETVRIREQVTTKRSKQELPPPPPPKKRQIPVDLEKLRDLQGAMDDLD  700
Human Microutro  651 DLLETVRVREQAITKKSKQELPPPPPPKKRQIHVDLEKLRDLQGAMDDLD  700
Mouse Microutro  651 DLLETVHVREQGMVKKPKQELPPPPPPKKRQIHVDLEKLRDLQGAMDDLD  700
                     ******..***   *. ***************** *****************

Canine Microutr  701 VDMKEAEAVRNGWKPVGDLLIDSLQDHIEKTMAFREEIAPINLKVKTVND  750
Human Microutro  701 ADMKEAESVRNGWKPVGDLLIDSLQDHIEKIMAFREEIAPINFKVKTVND  750
Mouse Microutro  701 ADMKEVEAVRNGWKPVGDLLIDSLQDHIEKTLAFREEIAPINLKVKTMND  750
                      **** *.********************** .********** ****.**

Canine Microutr  751 LSSQLSPLDLHPSLKMSRQLDDLNMRWKLLQVSVDDRLKQLQEAHRDFGP  800
Human Microutro  751 LSSQLSPLDLHPSLKMSRQLDDLNMRWKLLQVSVDDRLKQLQEAHRDFGP  800
Mouse Microutro  751 LSSQLSPLDLHPSLKMSRQLDDLNMRWKLLQVSVDDRLKQLQEAHRDFGP  800
                     **************************************************
```

FIG. 2D

```
Canine Microutr  801 SSQHFLSTSVQLPWQRSISHNKVPYYINHQTQTTCWDRPKMTELFQSLAD  850
Human Microutro  801 SSQHFLSTSVQLPWQRSISHNKVPYYINHQTQTTCWDHPKMTELFQSLAD  850
Mouse Microutro  801 SSQHFLSTSVQLPWQRSISHNKVPYYINHQTQTTCWDHPKMTELFQSLAD  850
                     ************************************.************

Canine Microutr  851 LNNVRFSAYRTAIKIRRLQKALCLDLLELNTTNEVFKQHKLNQNDQLLSV  900
Human Microutro  851 LNNVRFSAYRTAIKIRRLQKALCLDLLELSTTNEIFKQHKLNQNDQLLSV  900
Mouse Microutro  851 LNNVRFSAYRTAIKIRRLQKALCLDLLELNTTNEVFKQHKLNQNDQLLSV  900
                     ***************************** ****.***************

Canine Microutr  901 PDVINCLTTTYDGLEQMHKDLVNVPLCVDMCLNWLLNVYDTGRTGKIRVQ  950
Human Microutro  901 PDVINCLTTTYDGLEQMHKDLVNVPLCVDMCLNWLLNVYDTGRTGKIRVQ  950
Mouse Microutro  901 PDVINCLTTTYDGLEQLHKDLVNVPLCVDMCLNWLLNVYDTGRTGKIRVQ  950

Canine Microutr  951 SLKIGLMSLSKGLLEEKYRYLFKEVAGPTEMCDQRQLGLLLHDAIQIPRQ 1000
Human Microutro  951 SLKIGLMSLSKGLLEEKYRYLFKEVAGPTEMCDQRQLGLLLHDAIQIPRQ 1000
Mouse Microutro  951 SLKIGLMSLSKGLLEEKYRCLFKEVAGPTEMCDQRQLGLLLHDAIQIPRQ 1000
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Canine Microutr 1001 LGEVAAFGGSNIEPSVRSCFQQNNNKPEISVKDFIDWMRLEPQSMVWLPV 1050
Human Microutro 1001 LGEVAAFGGSNIEPSVRSCFQQNNNKPEISVKEFIDWMHLEPQSMVWLPV 1050
Mouse Microutro 1001 LGEVAAFGGSNIEPSVRSCFQQNNNKPEISVKEFIDWMHLEPQSMVWLPV 1050
                     ********************************.*****.***********

Canine Microutr 1051 LHRVAAAETAKHQAKCNICKECPIVGFRYRSLKHFNYDVCQSCFFSGRTA 1100
Human Microutro 1051 LHRVAAAETAKHQAKCNICKECPIVGFRYRSLKHFNYDVCQSCFFSGRTA 1100
Mouse Microutro 1051 LHRVAAAETAKHQAKCNICKECPIVGFRYRSLKHFNYDVCQSCFFSGRTA 1100
                     ************************************************
```

FIG. 2E

```
Canine Microutr 1101 KGHKLHYPMVEYCIPTTSGEDVRDFTKVLKNKFRSKKYFAKHPRLGYLPV 1150
Human Microutro 1101 KGHKLHYPMVEYCIPTTSGEDVRDFTKVLKNKFRSKKYFAKHPRLGYLPV 1150
Mouse Microutro 1101 KGHKLHYPMVEYCIPTTSGEDVRDFTKVLKNKFRSKKYFAKHPRLGYLPV 1150
                     **************************************************

Canine Microutr 1151 QTVLEGDNLETN 1162
Human Microutro 1151 QTVLEGDNLETN 1162
Mouse Microutro 1151 QTVLEGDNLETN 1162
                     ************
```

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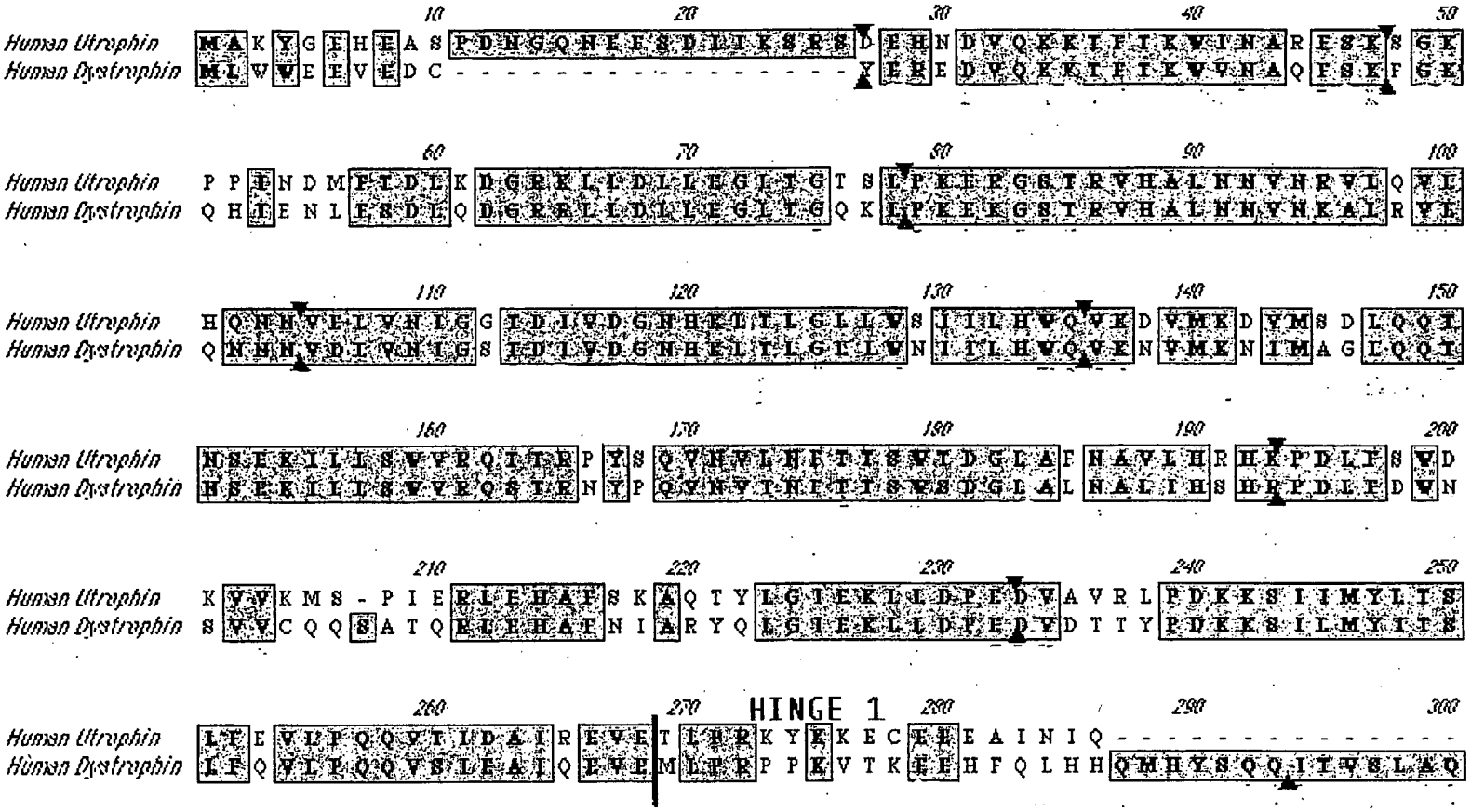

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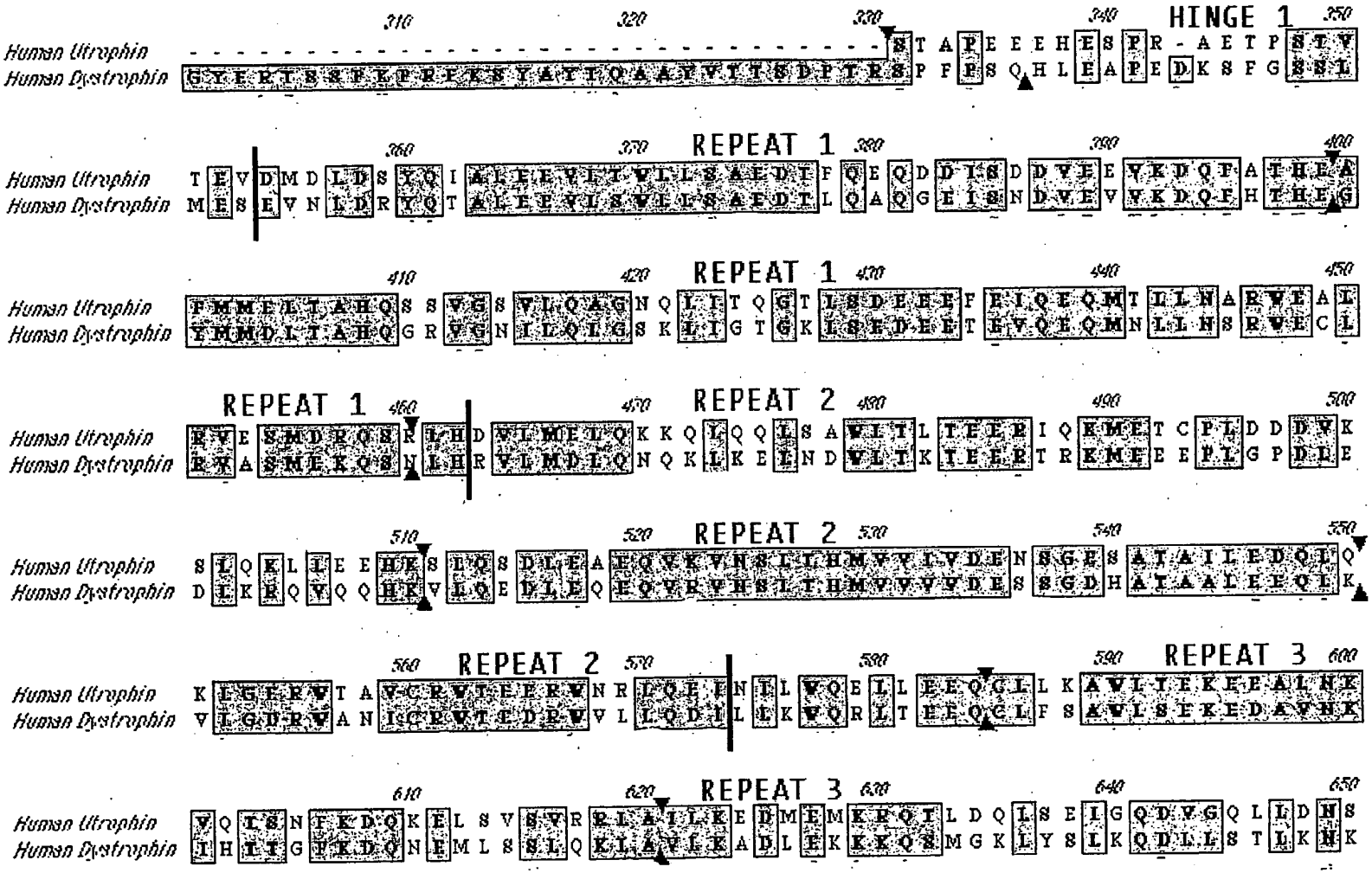
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REPEAT 1
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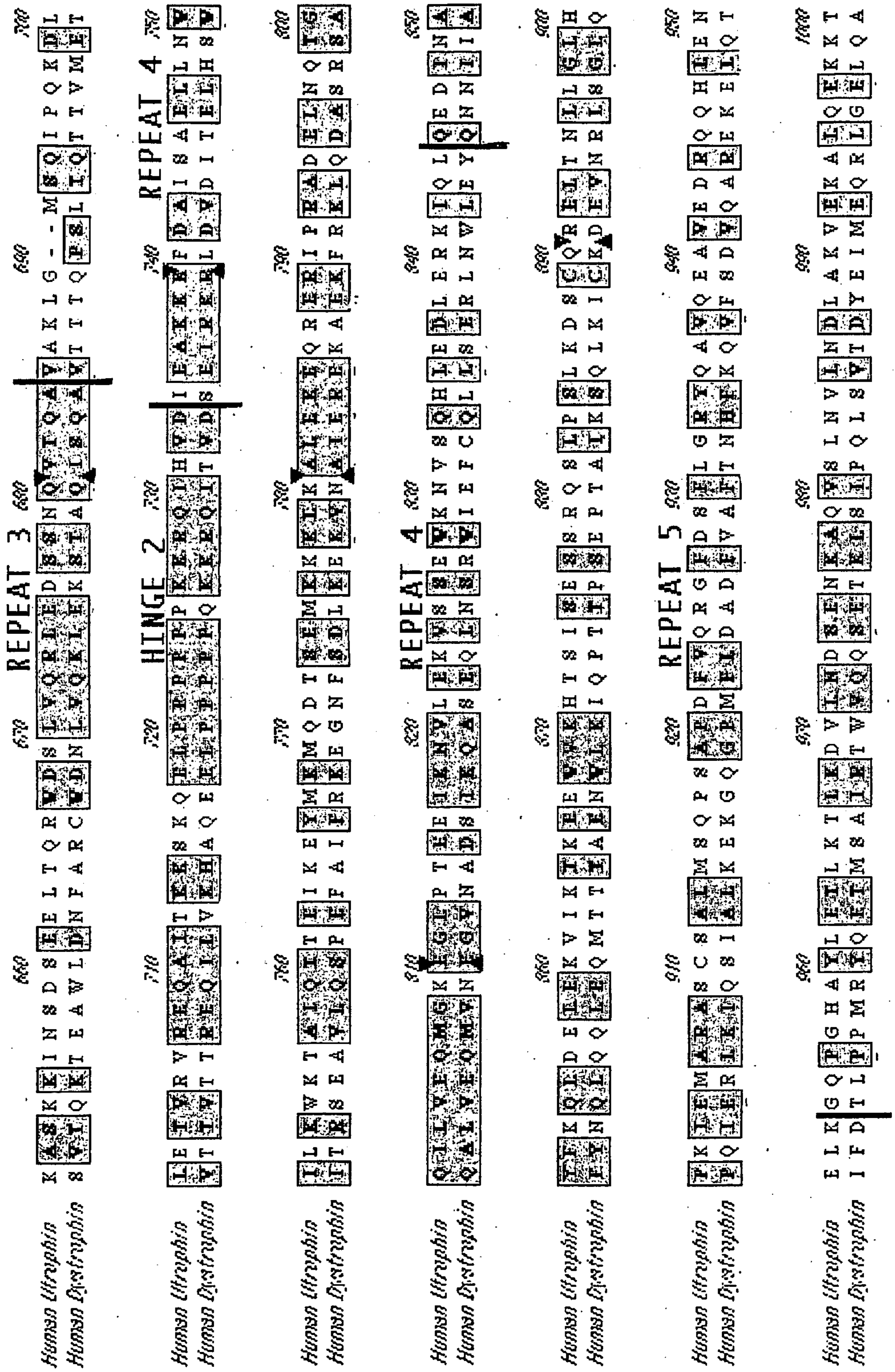
Human Dystrophin

FIG 3B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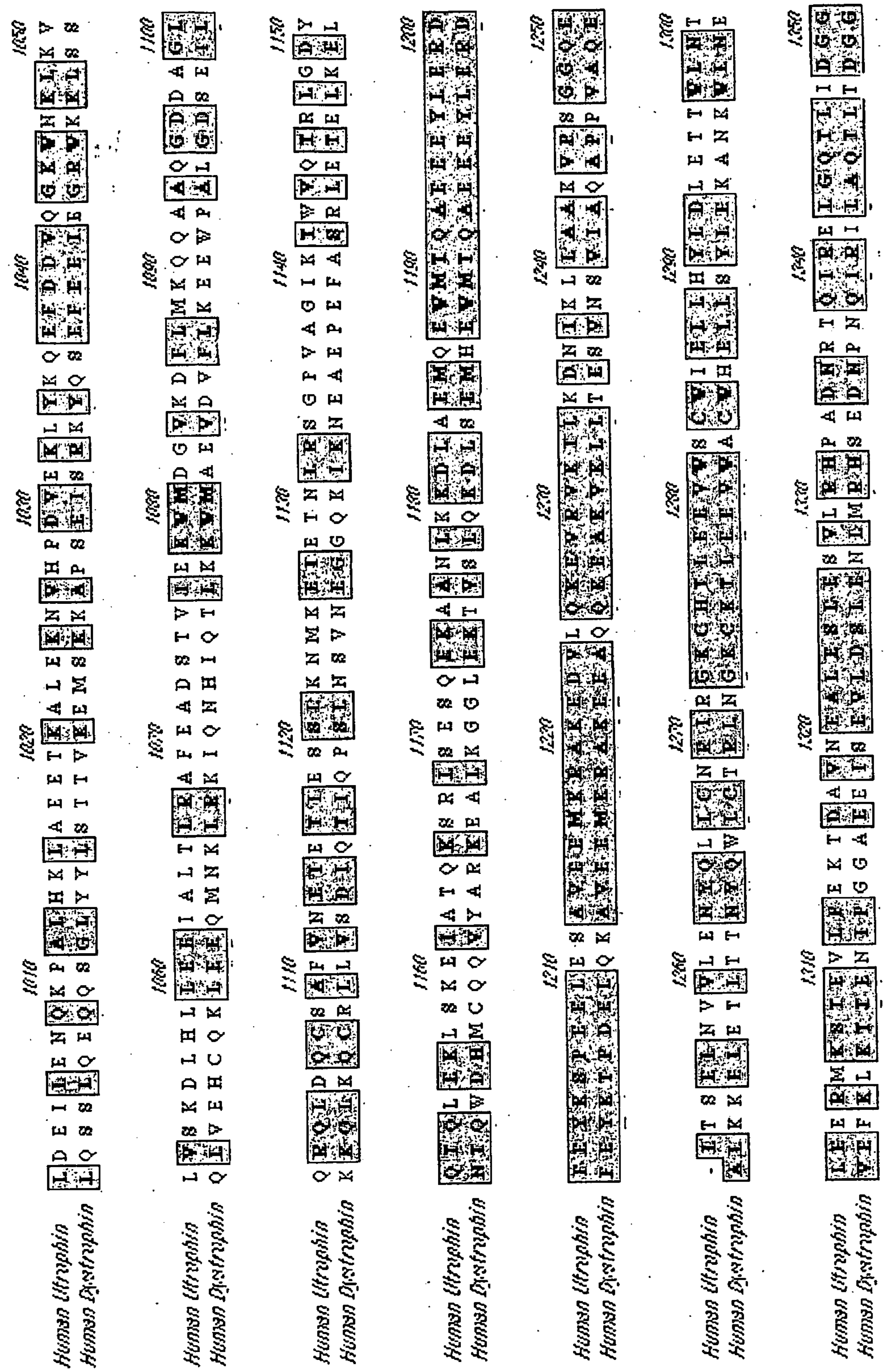
Human Dystrophin

FIG3C



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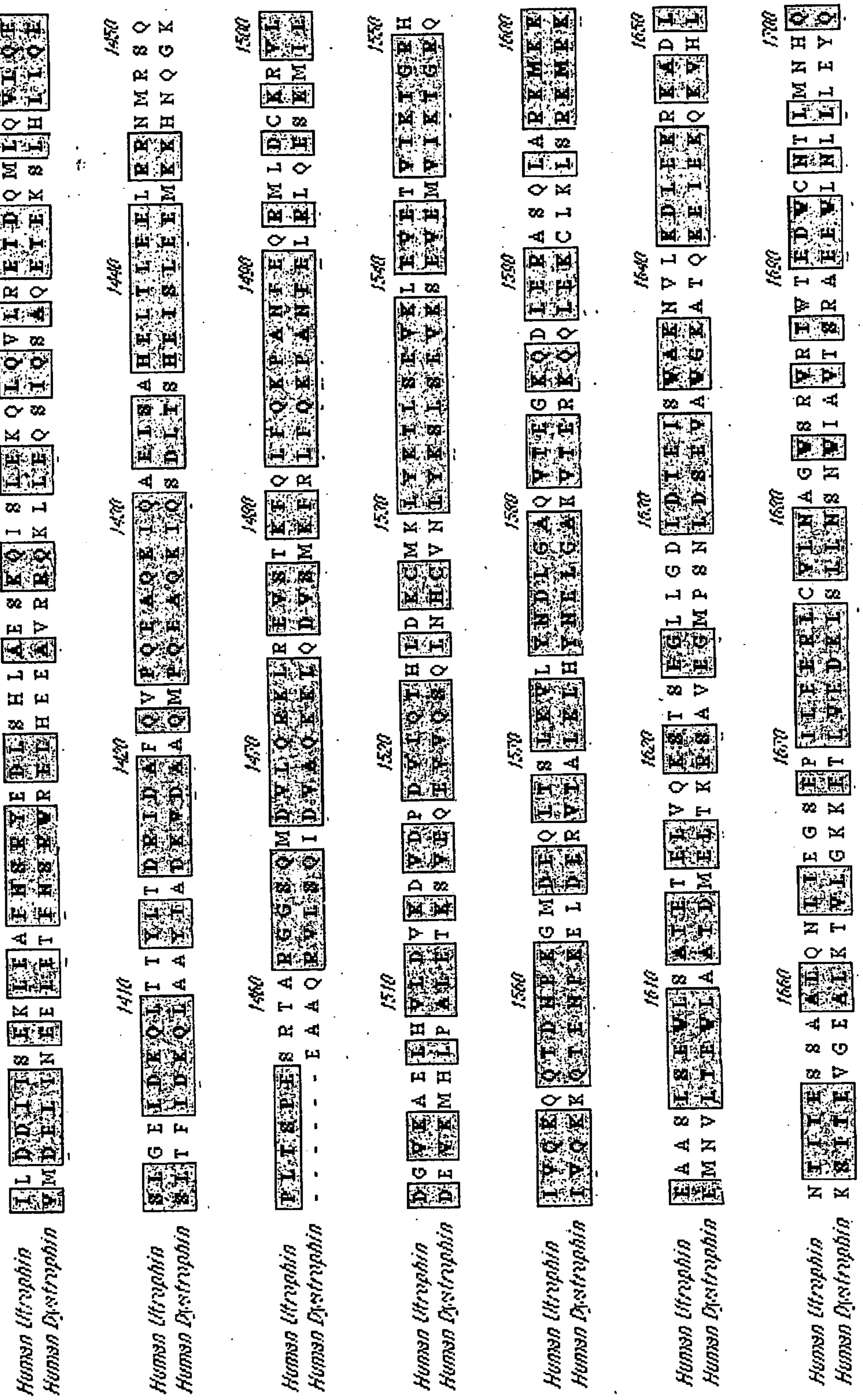

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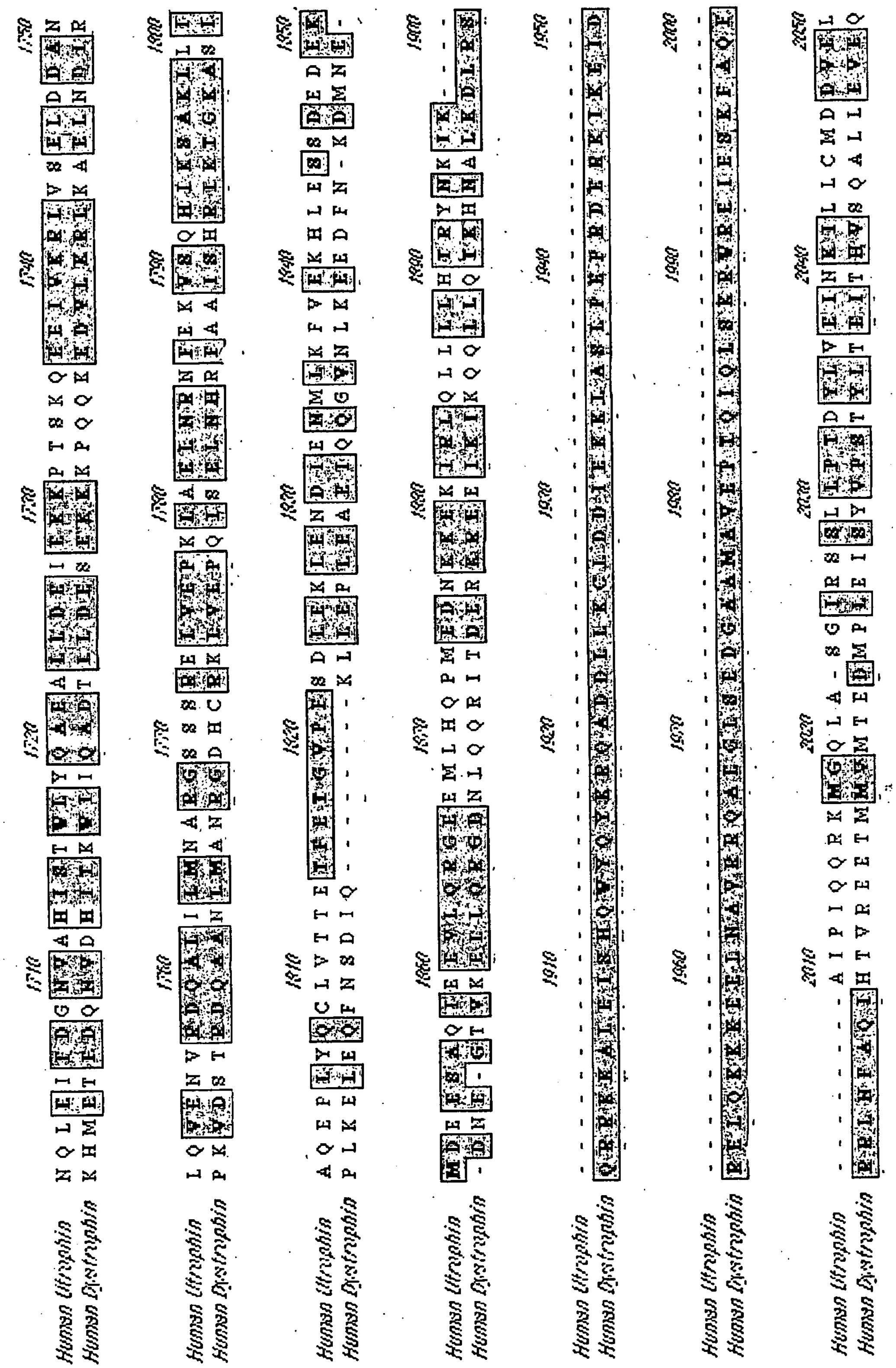

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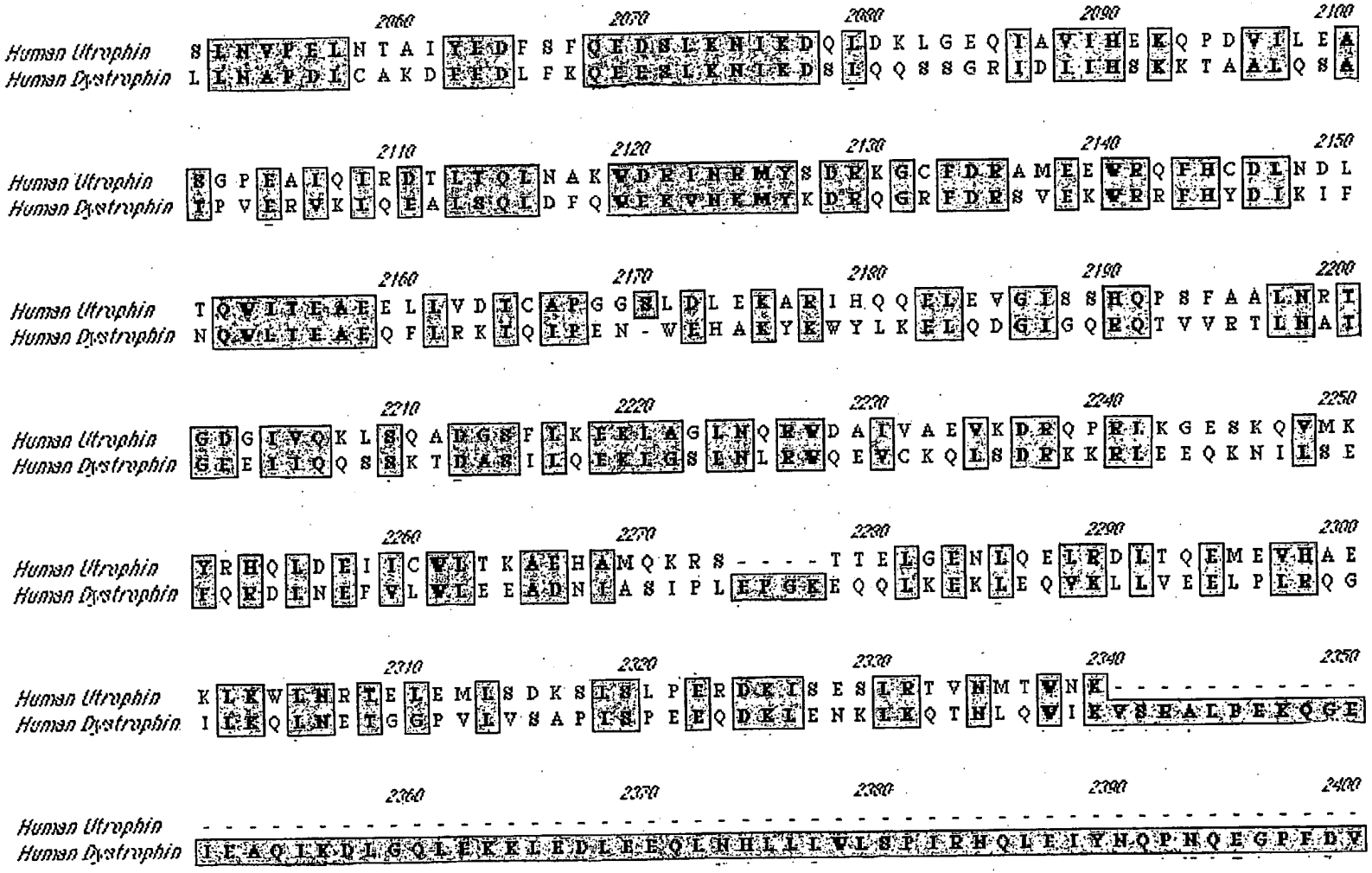
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2310
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2400
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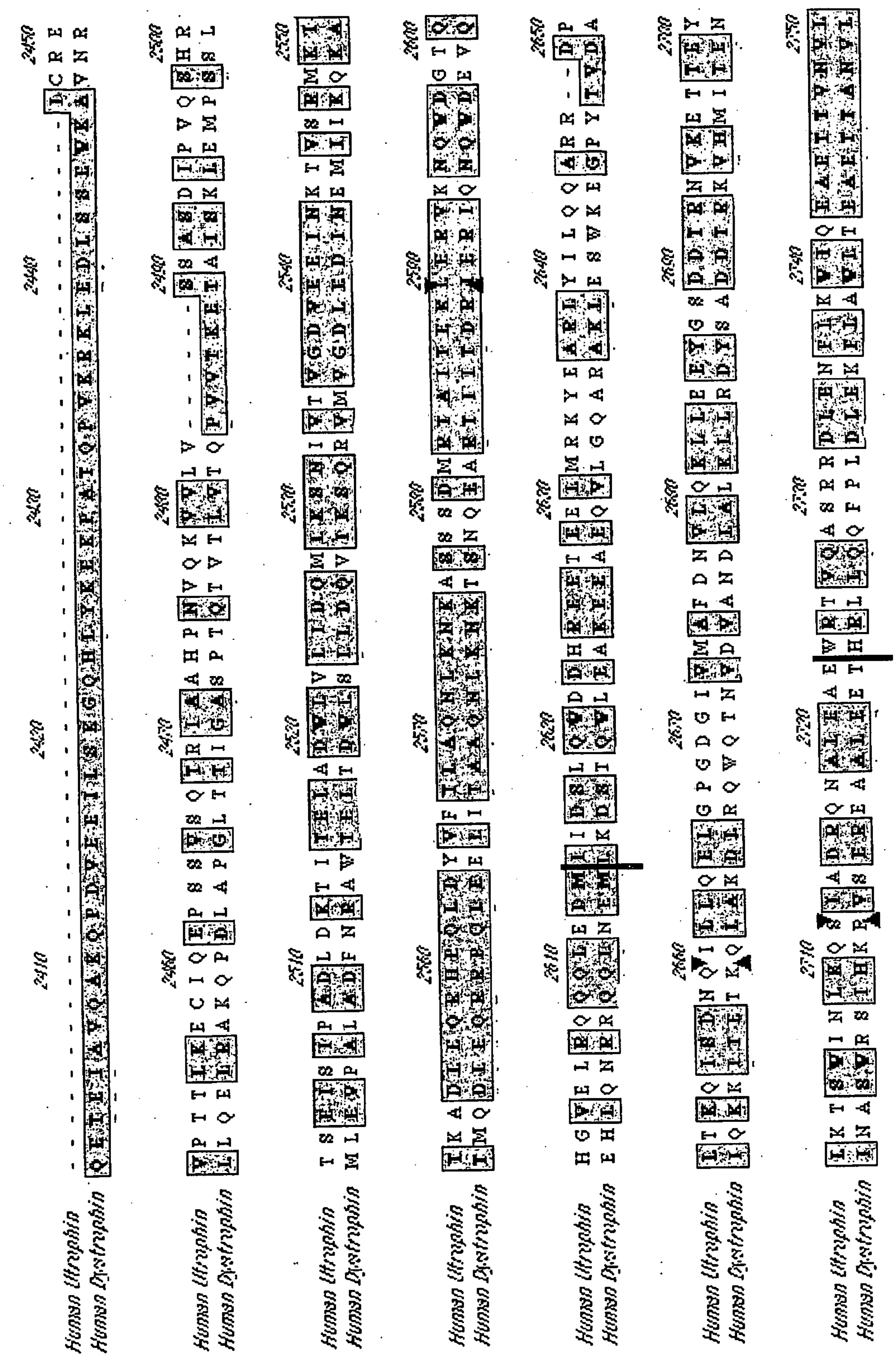
Human Dystrophin

FIG 3G



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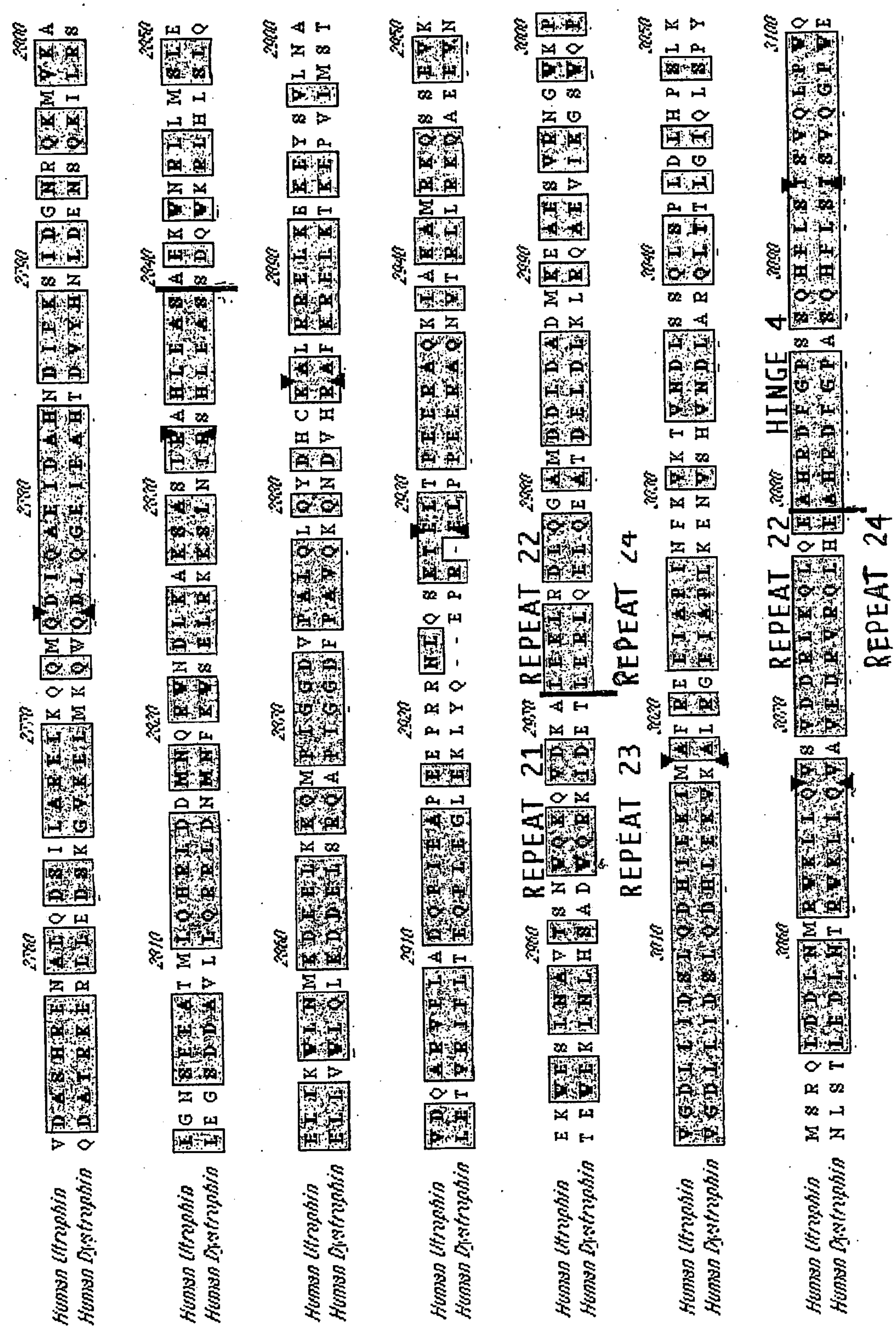
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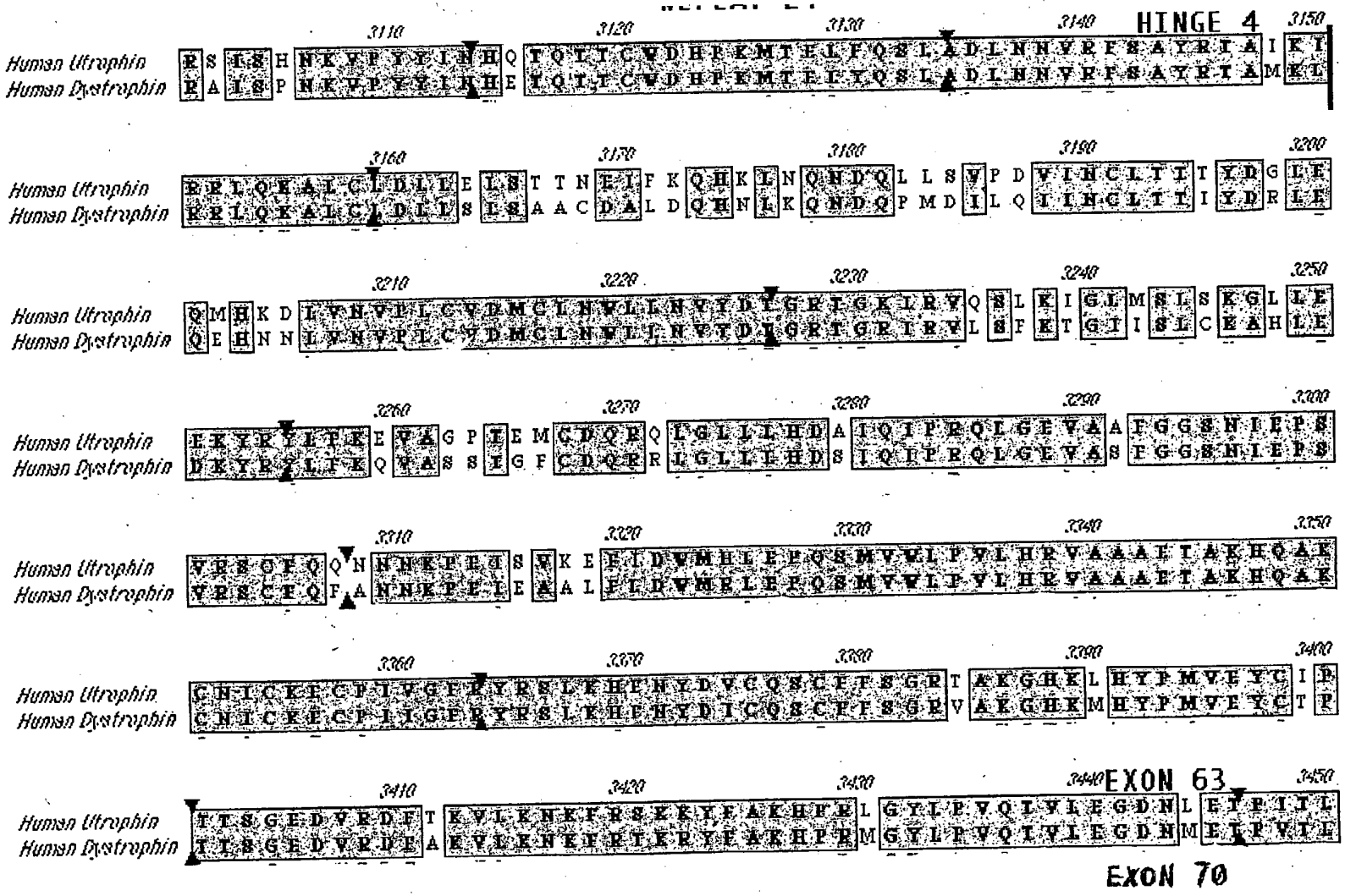
REPEAT 24
HINGE 4

FIG 3I



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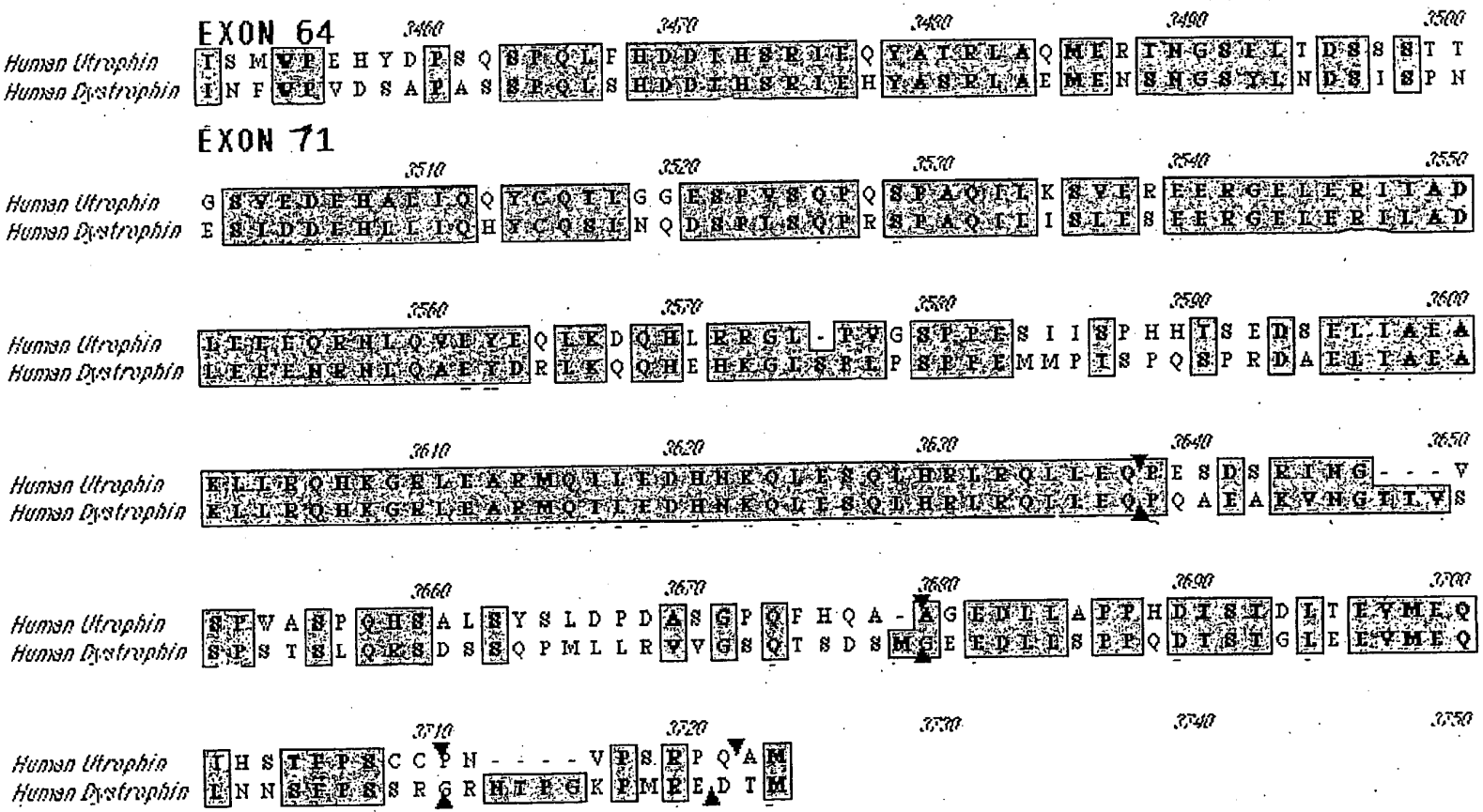

FIG 3k

SEQUENCE LISTING

<110> The Trustees of the University of Pennsylvania
Stedman, Hansell
Su, Leonard
Mitchell, Marilyn

<120> Microutrophin and Uses Thereof

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<151> 2004-01-23

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cactgccaaa ggaacgtggt tccacaaggg tacatgcttt aaataatgtc aacagagtgc 300

tgcaggtttt gcatcagaat aatgtggatt tagtgaatat aggaggaact gacattgtag 360

atggaaatca caaactgact ttgggattac tttggagcat cattttgcac tggcaggtaa 420

aagatgtcat gaaagatgtc atgtcagacc tgcagcagac aaacagtgag aagatcctac 480

tgagctgggt gcgccagtct actaggccgt acagccaggt caacgtcctc aacttcacca 540

ccagctggac agatggactg gcctttaatg ctgtgctgca ccgacataaa cctgatctct 600

tcagctggga tagagttgtc aaaatgtccc caattgagag acttgaacat gccttcagca 660

aagctcaaac ttatttggga attgaaaagc tgttagatcc tgaagatgtt gccgttcaac 720

ttcctgacaa gaaatccata attatgtatt taacatcttt gtttgaggtg cttcctcagc 780

aagtcactct agatgccatc cgtgaagtag agacactccc aaggaaatat aagaaagaat 840

gtgaagaagg agagattagt atacagagct cagcgccaga ggaggagcat gagtgtcccg 900

gagctgaaac ccccagcact gtcactgaag ttgacacgga tctggacagc tatcagatag 960

cactggagga agtgctgacc tggttgcttt ctgccgagga cactttccag gagcaggatg 1020

acatttctga tgatgtagaa gaagtcaaag agcagtttac tacccatgaa gcttttatga 1080

tggagctgac agcgcaccag agcagtgtgg gcagtgtcct gcaggcagga aaccagctga 1140

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taaatgctag atgggaggca ctcagggtgg atagtatgaa cagacagtcc cggctgcatg 1260
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attttgggcc atcctctcag cattttcttt ctacttcagt ccagctgcca tggcaaagat 2460
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tccctcggca gctgggggaa gtagcagctt ttgggggcag taatattgaa cccagtgttc 3060
gcagctgctt ccaacagaat aacaataagc cagagataag cgtaaaagat tttatagatt 3120

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ctgagactgc aaagcatcaa gctaaatgca acatctgtaa agaatgtcca atagttgggt 3240

tcaggtatag aagcctaaag cattttaact atgatgtctg ccagagttgc ttttttttcgg 3300

gtcgaacggc aaaaggtcac aaattacatt acccaatggt ggaatattgt atacctacaa 3360

catctgggga agatgtacga gacttcacaa aggtgctgaa gaataagttc agatcaaaga 3420

aatactttgc caaacatcct cggcttggct acctgcctgt ccagacagta cttgaaggtg 3480

acaacttaga gacttgaaaa actcgag 3507

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<212> PRT
<213> Artificial

<220>
<223> Canine Microutrophin

<400> 2

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Glu Phe Ser Asp Ile Ile Lys Ser Arg Ser Asp Glu His Asn Asp Val
20 25 30

Gln Lys Lys Thr Phe Thr Lys Trp Ile Asn Ala Arg Phe Ser Lys Ser
35 40 45

Gly Lys Pro Pro Ile Asn Asp Met Phe Thr Asp Leu Lys Asp Gly Arg
50 55 60

Lys Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Thr Ser Leu Pro Lys
65 70 75 80

Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
85 90 95

Leu Gln Val Leu His Gln Asn Asn Val Asp Leu Val Asn Ile Gly Gly
100 105 110

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Leu Trp
115 120 125

Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Val Met
130 135 140

Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
145 150 155 160

Arg Gln Ser Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
165 170 175

Thr Ser Trp Thr Asp Gly Leu Ala Phe Asn Ala Val Leu His Arg His
180 185 190

Lys Pro Asp Leu Phe Ser Trp Asp Arg Val Val Lys Met Ser Pro Ile
195 200 205

Glu Arg Leu Glu His Ala Phe Ser Lys Ala Gln Thr Tyr Leu Gly Ile
210 215 220

Glu Lys Leu Leu Asp Pro Glu Asp Val Ala Val Gln Leu Pro Asp Lys
225 230 235 240

Lys Ser Ile Ile Met Tyr Leu Thr Ser Leu Phe Glu Val Leu Pro Gln
245 250 255

Gln Val Thr Leu Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Gly Glu Ile Ser Ile Gln Ser Ser Ala
275 280 285

Pro Glu Glu Glu His Glu Cys Pro Gly Ala Glu Thr Pro Ser Thr Val
290 295 300

Thr Glu Val Asp Thr Asp Leu Asp Ser Tyr Gln Ile Ala Leu Glu Glu
305 310 315 320

Val Leu Thr Trp Leu Leu Ser Ala Glu Asp Thr Phe Gln Glu Gln Asp
325 330 335

Asp Ile Ser Asp Asp Val Glu Glu Val Lys Glu Gln Phe Thr Thr His
340 345 350

Glu Ala Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
355 360 365

Val Leu Gln Ala Gly Asn Gln Leu Ile Thr Gln Gly Thr Leu Ser Asp
370 375 380

Glu Glu Glu Phe Glu Ile Gln Glu Gln Met Thr Leu Leu Asn Ala Arg
385 390 395 400

Trp Glu Ala Leu Arg Val Asp Ser Met Asn Arg Gln Ser Arg Leu His
405 410 415

Asp Val Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ala
420 425 430

Trp Leu Thr Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Thr Cys Pro
435 440 445

Leu Asp Asp Asp Leu Lys Ser Leu Gln Lys Leu Leu Glu Asp His Lys
450 455 460

Arg Leu Gln Asn Asp Leu Glu Ala Glu Gln Val Lys Val Asn Ser Leu
465 470 475 480

Thr His Met Val Val Ile Val Asp Glu Asn Ser Gly Glu Ser Ala Thr
485 490 495

Ala Val Leu Glu Asp Gln Leu Gln Lys Leu Gly Glu Arg Trp Thr Ala
500 505 510

Val Cys Arg Trp Thr Glu Glu Arg Trp Ser Arg Leu Gln Glu Ile Asn
515 520 525

Ile Leu Trp Gln Glu Leu Leu Glu Glu Gln Cys Leu Leu Lys Ala Trp
530 535 540

Leu Thr Glu Lys Glu Glu Ala Leu Asn Lys Val Gln Thr Ser Asn Phe
545 550 555 560

Lys Asp Gln Lys Glu Leu Ser Val Ser Ile Arg Arg Leu Ala Ile Leu
565 570 575

Lys Glu Asp Met Glu Met Lys Arg Gln Ala Leu Asp Gln Leu Ser Glu
580 585 590

Ile Gly Gln Asp Val Gly Gln Leu Val Asp Asn Pro Lys Ala Ser Lys
595 600 605

Lys Ile Asn Ser Asp Ser Glu Glu Leu Thr Gln Arg Trp Asp Ser Leu
610 615 620

Val Gln Arg Leu Glu Asp Ser Ser Asn Gln Val Thr Gln Ala Val Ala
625 630 635 640

Lys Leu Gly Met Ser Gln Ile Pro Gln Lys Asp Leu Leu Glu Thr Val
645 650 655

Arg Ile Arg Glu Gln Val Thr Thr Lys Arg Ser Lys Gln Glu Leu Pro
660 665 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile Pro Val Asp Leu Glu Lys

675 680 685

Leu Arg Asp Leu Gln Gly Ala Met Asp Asp Leu Asp Val Asp Met Lys
690 695 700

Glu Ala Glu Ala Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
705 710 715 720

Ile Asp Ser Leu Gln Asp His Ile Glu Lys Thr Met Ala Phe Arg Glu
725 730 735

Glu Ile Ala Pro Ile Asn Leu Lys Val Lys Thr Val Asn Asp Leu Ser
740 745 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
755 760 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val
770 775 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785 790 795 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
805 810 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
820 825 830

Thr Thr Cys Trp Asp Arg Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
835 840 845

Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Ile Lys
850 855 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Asn
865 870 875 880

Thr Thr Asn Glu Val Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
885 890 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
900 905 910

Gly Leu Glu Gln Met His Lys Asp Leu Val Asn Val Pro Leu Cys Val
915 920 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
930 935 940

Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
945 950 955 960

Lys Gly Leu Leu Glu Glu Lys Tyr Arg Tyr Leu Phe Lys Glu Val Ala
965 970 975

Gly Pro Thr Glu Met Cys Asp Gln Arg Gln Leu Gly Leu Leu Leu His
980 985 990

Asp Ala Ile Gln Ile Pro Arg Gln Leu Gly Glu Val Ala Ala Phe Gly
995 1000 1005

Gly Ser Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Gln Asn
1010 1015 1020

Asn Asn Lys Pro Glu Ile Ser Val Lys Asp Phe Ile Asp Trp Met
1025 1030 1035

Arg Leu Glu Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg
1040 1045 1050

Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile
1055 1060 1065

Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser Leu Lys
1070 1075 1080

His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly Arg
1085 1090 1095

Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys
1100 1105 1110

Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
1115 1120 1125

Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
1130 1135 1140

Arg Leu Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn
1145 1150 1155

Leu Glu Thr Asn
1160

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<211> 988
<212> PRT

<213> Human Utrophin

<400> 3

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1 5 10 15

Ala Val Val Arg Thr Ser Leu Gln Lys Val Val Val Leu Leu His Arg
20 25 30

Leu Gln Arg Met Ala Val Ser Ser Pro Arg Tyr Gln Lys Leu Cys Lys
35 40 45

Asp Ile Gln Ala Glu Ile Asp Ala His Asn Asp Ile Phe Lys Ser Ile
50 55 60

Asp Gly Asn Arg Gln Lys Met Val Lys Ala Leu Gly Asn Ser Glu Glu
65 70 75 80

Ala Thr Met Leu Gln His Arg Leu Asp Asp Met Asn Gln Arg Trp Asn
85 90 95

Asp Leu Lys Ala Lys Ser Ala Ser Ile Arg Ala His Leu Glu Ala Ser
100 105 110

Ala Glu Lys Trp Asn Arg Leu Leu Met Ser Leu Glu Glu Leu Ile Lys
115 120 125

Trp Leu Asn Met Lys Asp Glu Glu Leu Lys Lys Gln Met Pro Ile Gly
130 135 140

Gly Asp Val Pro Ala Leu Gln Leu Gln Tyr Asp His Cys Lys Ala Leu
145 150 155 160

Arg Arg Glu Leu Lys Glu Lys Glu Tyr Ser Val Leu Asn Ala Val Asp
165 170 175

Gln Ala Arg Val Phe Leu Ala Asp Gln Pro Ile Glu Ala Pro Glu Glu
180 185 190

Pro Arg Arg Asn Leu Gln Ser Lys Thr Glu Leu Thr Pro Glu Glu Arg
195 200 205

Ala Gln Lys Ile Ala Lys Ala Met Arg Lys Gln Ser Ser Glu Val Lys
210 215 220

Glu Lys Trp Glu Ser Leu Asn Ala Val Thr Ser Asn Trp Gln Lys Gln
225 230 235 240

Val Asp Lys Ala Leu Glu Lys Leu Arg Asp Leu Gln Gly Ala Met Asp

245 250 255

Asp Leu Asp Ala Asp Met Lys Glu Ala Glu Ser Val Arg Asn Gly Trp
260 265 270

Lys Pro Val Gly Asp Leu Leu Ile Asp Ser Leu Gln Asp His Ile Glu
275 280 285

Lys Ile Met Ala Phe Arg Glu Glu Ile Ala Pro Ile Asn Phe Lys Val
290 295 300

Lys Thr Val Asn Asp Leu Ser Ser Gln Leu Ser Pro Leu Asp Leu His
305 310 315 320

Pro Ser Leu Lys Met Ser Arg Gln Leu Asp Asp Leu Asn Met Arg Trp
325 330 335

Lys Leu Leu Gln Val Ser Val Asp Asp Arg Leu Lys Gln Leu Gln Glu
340 345 350

Ala His Arg Asp Phe Gly Pro Ser Ser Gln His Phe Leu Ser Thr Ser
355 360 365

Val Gln Leu Pro Trp Gln Arg Ser Ile Ser His Asn Lys Val Pro Tyr
370 375 380

Tyr Ile Asn His Gln Thr Gln Thr Thr Cys Trp Asp His Pro Lys Met
385 390 395 400

Thr Glu Leu Phe Gln Ser Leu Ala Asp Leu Asn Asn Val Arg Phe Ser
405 410 415

Ala Tyr Arg Thr Ala Ile Lys Ile Arg Arg Leu Gln Lys Ala Leu Cys
420 425 430

Leu Asp Leu Leu Glu Leu Ser Thr Thr Asn Glu Ile Phe Lys Gln His
435 440 445

Lys Leu Asn Gln Asn Asp Gln Leu Leu Ser Val Pro Asp Val Ile Asn
450 455 460

Cys Leu Thr Thr Thr Tyr Asp Gly Leu Glu Gln Met His Lys Asp Leu
465 470 475 480

Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn Trp Leu Leu Asn
485 490 495

Val Tyr Asp Thr Gly Arg Thr Gly Lys Ile Arg Val Gln Ser Leu Lys
500 505 510

Ile Gly Leu Met Ser Leu Ser Lys Gly Leu Leu Glu Glu Lys Tyr Arg
515 520 525

Tyr Leu Phe Lys Glu Val Ala Gly Pro Thr Glu Met Cys Asp Gln Arg
530 535 540

Gln Leu Gly Leu Leu Leu His Asp Ala Ile Gln Ile Pro Arg Gln Leu
545 550 555 560

Gly Glu Val Ala Ala Phe Gly Gly Ser Asn Ile Glu Pro Ser Val Arg
565 570 575

Ser Cys Phe Gln Gln Asn Asn Asn Lys Pro Glu Ile Ser Val Lys Glu
580 585 590

Phe Ile Asp Trp Met His Leu Glu Pro Gln Ser Met Val Trp Leu Pro
595 600 605

Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys
610 615 620

Cys Asn Ile Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser
625 630 635 640

Leu Lys His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly
645 650 655

Arg Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys
660 665 670

Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val Leu
675 680 685

Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro Arg Leu
690 695 700

Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn Leu Glu Thr
705 710 715 720

Pro Ile Thr Leu Ile Ser Met Trp Pro Glu His Tyr Asp Pro Ser Gln
725 730 735

Ser Pro Gln Leu Phe His Asp Asp Thr His Ser Arg Ile Glu Gln Tyr
740 745 750

Ala Thr Arg Leu Ala Gln Met Glu Arg Thr Asn Gly Ser Phe Leu Thr
755 760 765

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Asp Ser Ser Ser Thr Thr Gly Ser Val Glu Asp Glu His Ala Leu Ile
    770                 775                 780

Gln Gln Tyr Cys Gln Thr Leu Gly Gly Glu Ser Pro Val Ser Gln Pro
785                 790                 795                 800

Gln Ser Pro Ala Gln Ile Leu Lys Ser Val Glu Arg Glu Glu Arg Gly
                805                 810                 815

Glu Leu Glu Arg Ile Ile Ala Asp Leu Glu Glu Glu Gln Arg Asn Leu
            820                 825                 830

Gln Val Glu Tyr Glu Gln Leu Lys Asp Gln His Leu Arg Arg Gly Leu
        835                 840                 845

Pro Val Gly Ser Pro Pro Glu Ser Ile Ile Ser Pro His His Thr Ser
    850                 855                 860

Glu Asp Ser Glu Leu Ile Ala Glu Ala Lys Leu Leu Arg Gln His Lys
865                 870                 875                 880

Gly Arg Leu Glu Ala Arg Met Gln Ile Leu Glu Asp His Asn Lys Gln
                885                 890                 895

Leu Glu Ser Gln Leu His Arg Leu Arg Gln Leu Leu Glu Gln Pro Glu
            900                 905                 910

Ser Asp Ser Arg Ile Asn Gly Val Ser Pro Trp Ala Ser Pro Gln His
        915                 920                 925

Ser Ala Leu Ser Tyr Ser Leu Asp Pro Asp Ala Ser Gly Pro Gln Phe
    930                 935                 940

His Gln Ala Ala Gly Glu Asp Leu Leu Ala Pro Pro His Asp Thr Ser
945                 950                 955                 960

Thr Asp Leu Thr Glu Val Met Glu Gln Ile His Ser Thr Phe Pro Ser
                965                 970                 975

Cys Cys Pro Asn Val Pro Ser Arg Pro Gln Ala Met
            980                 985
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<211> 1162
<212> PRT
<213> artificial

<220>
<223> human microutrophin

<400> 4

Met Ala Lys Tyr Gly Glu His Glu Ala Ser Pro Asp Asn Gly Gln Asn
1 5 10 15

Glu Phe Ser Asp Ile Ile Lys Ser Arg Ser Asp Glu His Asn Asp Val
20 25 30

Gln Lys Lys Thr Phe Thr Lys Trp Ile Asn Ala Arg Phe Ser Lys Ser
35 40 45

Gly Lys Pro Pro Ile Asn Asp Met Phe Thr Asp Leu Lys Asp Gly Arg
50 55 60

Lys Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Thr Ser Leu Pro Lys
65 70 75 80

Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
85 90 95

Leu Gln Val Leu His Gln Asn Asn Val Glu Leu Val Asn Ile Gly Gly
100 105 110

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Leu Trp
115 120 125

Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Val Met
130 135 140

Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
145 150 155 160

Arg Gln Thr Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
165 170 175

Thr Ser Trp Thr Asp Gly Leu Ala Phe Asn Ala Val Leu His Arg His
180 185 190

Lys Pro Asp Leu Phe Ser Trp Asp Lys Val Val Lys Met Ser Pro Ile
195 200 205

Glu Arg Leu Glu His Ala Phe Ser Lys Ala Gln Thr Tyr Leu Gly Ile
210 215 220

Glu Lys Leu Leu Asp Pro Glu Asp Val Ala Val Arg Leu Pro Asp Lys
225 230 235 240

Lys Ser Ile Ile Met Tyr Leu Thr Ser Leu Phe Glu Val Leu Pro Gln
245 250 255

Gln Val Thr Ile Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Glu Ala Ile Asn Ile Gln Ser Thr Ala
275 280 285

Pro Glu Glu Glu His Glu Ser Pro Arg Ala Glu Thr Pro Ser Thr Val
290 295 300

Thr Glu Val Asp Met Asp Leu Asp Ser Tyr Gln Ile Ala Leu Glu Glu
305 310 315 320

Val Leu Thr Trp Leu Leu Ser Ala Glu Asp Thr Phe Gln Glu Gln Asp
325 330 335

Asp Ile Ser Asp Asp Val Glu Glu Val Lys Asp Gln Phe Ala Thr His
340 345 350

Glu Ala Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
355 360 365

Val Leu Gln Ala Gly Asn Gln Leu Ile Thr Gln Gly Thr Leu Ser Asp
370 375 380

Glu Glu Glu Phe Glu Ile Gln Glu Gln Met Thr Leu Leu Asn Ala Arg
385 390 395 400

Trp Glu Ala Leu Arg Val Glu Ser Met Asp Arg Gln Ser Arg Leu His
405 410 415

Asp Val Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ala
420 425 430

Trp Leu Thr Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Thr Cys Pro
435 440 445

Leu Asp Asp Asp Val Lys Ser Leu Gln Lys Leu Leu Glu Glu His Lys
450 455 460

Ser Leu Gln Ser Asp Leu Glu Ala Glu Gln Val Lys Val Asn Ser Leu
465 470 475 480

Thr His Met Val Val Ile Val Asp Glu Asn Ser Gly Glu Ser Ala Thr
485 490 495

Ala Ile Leu Glu Asp Gln Leu Gln Lys Leu Gly Glu Arg Trp Thr Ala
500 505 510

Val Cys Arg Trp Thr Glu Glu Arg Trp Asn Arg Leu Gln Glu Ile Asn
515 520 525

Ile Leu Trp Gln Glu Leu Leu Glu Glu Gln Cys Leu Leu Lys Ala Trp
530 535 540

Leu Thr Glu Lys Glu Glu Ala Leu Asn Lys Val Gln Thr Ser Asn Phe
545 550 555 560

Lys Asp Gln Lys Glu Leu Ser Val Ser Val Arg Arg Leu Ala Ile Leu
565 570 575

Lys Glu Asp Met Glu Met Lys Arg Gln Thr Leu Asp Gln Leu Ser Glu
580 585 590

Ile Gly Gln Asp Val Gly Gln Leu Leu Asp Asn Ser Lys Ala Ser Lys
595 600 605

Lys Ile Asn Ser Asp Ser Glu Glu Leu Thr Gln Arg Trp Asp Ser Leu
610 615 620

Val Gln Arg Leu Glu Asp Ser Ser Asn Gln Val Thr Gln Ala Val Ala
625 630 635 640

Lys Leu Gly Met Ser Gln Ile Pro Gln Lys Asp Leu Leu Glu Thr Val
645 650 655

Arg Val Arg Glu Gln Ala Ile Thr Lys Lys Ser Lys Gln Glu Leu Pro
660 665 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile His Val Asp Leu Glu Lys
675 680 685

Leu Arg Asp Leu Gln Gly Ala Met Asp Asp Leu Asp Ala Asp Met Lys
690 695 700

Glu Ala Glu Ser Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
705 710 715 720

Ile Asp Ser Leu Gln Asp His Ile Glu Lys Ile Met Ala Phe Arg Glu
725 730 735

Glu Ile Ala Pro Ile Asn Phe Lys Val Lys Thr Val Asn Asp Leu Ser
740 745 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
755 760 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val

770 775 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785 790 795 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
805 810 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
820 825 830

Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
835 840 845

Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Ile Lys
850 855 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Ser
865 870 875 880

Thr Thr Asn Glu Ile Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
885 890 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
900 905 910

Gly Leu Glu Gln Met His Lys Asp Leu Val Asn Val Pro Leu Cys Val
915 920 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
930 935 940

Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
945 950 955 960

Lys Gly Leu Leu Glu Glu Lys Tyr Arg Tyr Leu Phe Lys Glu Val Ala
965 970 975

Gly Pro Thr Glu Met Cys Asp Gln Arg Gln Leu Gly Leu Leu Leu His
980 985 990

Asp Ala Ile Gln Ile Pro Arg Gln Leu Gly Glu Val Ala Ala Phe Gly
995 1000 1005

Gly Ser Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Gln Asn
1010 1015 1020

Asn Asn Lys Pro Glu Ile Ser Val Lys Glu Phe Ile Asp Trp Met
1025 1030 1035

His Leu Glu Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg
1040 1045 1050

Val Ala Ala Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile
1055 1060 1065

Cys Lys Glu Cys Pro Ile Val Gly Phe Arg Tyr Arg Ser Leu Lys
1070 1075 1080

His Phe Asn Tyr Asp Val Cys Gln Ser Cys Phe Phe Ser Gly Arg
1085 1090 1095

Thr Ala Lys Gly His Lys Leu His Tyr Pro Met Val Glu Tyr Cys
1100 1105 1110

Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
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Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
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Gly Lys Pro Pro Ile Ser Asp Met Phe Ser Asp Leu Lys Asp Gly Arg
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Lys Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Thr Ser Leu Pro Lys

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Glu Arg Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Arg Val
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Leu Gln Val Leu His Gln Asn Asn Val Asp Leu Val Asn Ile Gly Gly
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Thr Asp Ile Val Ala Gly Asn Pro Lys Leu Thr Leu Gly Leu Leu Trp
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Ser Ile Ile Leu His Trp Gln Val Lys Asp Val Met Lys Asp Ile Met
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Ser Asp Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Thr Thr Arg Pro Tyr Ser Gln Val Asn Val Leu Asn Phe Thr
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Thr Ser Trp Thr Asp Gly Leu Ala Phe Asn Ala Val Leu His Arg His
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Lys Pro Asp Leu Phe Asp Trp Asp Glu Met Val Lys Met Ser Pro Ile
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Glu Arg Leu Asp His Ala Phe Asp Lys Ala His Thr Ser Leu Gly Ile
210 215 220

Glu Lys Leu Leu Ser Pro Glu Thr Val Ala Val His Leu Pro Asp Lys
225 230 235 240

Lys Ser Ile Ile Met Tyr Leu Thr Ser Leu Phe Glu Val Leu Pro Gln
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Gln Val Thr Ile Asp Ala Ile Arg Glu Val Glu Thr Leu Pro Arg Lys
260 265 270

Tyr Lys Lys Glu Cys Glu Glu Glu Glu Ile His Ile Gln Ser Ala Val
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Leu Ala Glu Glu Gly Gln Ser Pro Arg Ala Glu Thr Pro Ser Thr Val
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Thr Glu Val Asp Met Asp Leu Asp Ser Tyr Gln Ile Ala Leu Glu Glu
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Val Leu Thr Trp Leu Leu Ser Ala Glu Asp Thr Phe Gln Glu Gln His
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Asp Ile Ser Asp Asp Val Glu Glu Val Lys Glu Gln Phe Ala Thr His
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Glu Thr Phe Met Met Glu Leu Thr Ala His Gln Ser Ser Val Gly Ser
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Val Leu Gln Ala Gly Asn Gln Leu Met Thr Gln Gly Thr Leu Ser Arg
    370                 375                 380

Glu Glu Glu Phe Glu Ile Gln Glu Gln Met Thr Leu Leu Asn Ala Arg
385                 390                 395                 400

Trp Glu Ala Leu Arg Val Glu Ser Met Glu Arg Gln Ser Arg Leu His
                405                 410                 415

Asp Ala Leu Met Glu Leu Gln Lys Lys Gln Leu Gln Gln Leu Ser Ser
            420                 425                 430

Trp Leu Ala Leu Thr Glu Glu Arg Ile Gln Lys Met Glu Ser Leu Pro
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Leu Gly Asp Asp Leu Pro Ser Leu Gln Lys Leu Leu Gln Glu His Lys
    450                 455                 460

Ser Leu Gln Asn Asp Leu Glu Ala Glu Gln Val Lys Val Asn Ser Leu
465                 470                 475                 480

Thr His Met Val Val Ile Val Asp Glu Asn Ser Gly Glu Ser Ala Thr
                485                 490                 495

Ala Leu Leu Glu Asp Gln Leu Gln Lys Leu Gly Glu Arg Trp Thr Ala
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Val Cys Arg Trp Thr Glu Glu Arg Trp Asn Arg Leu Gln Glu Ile Ser
        515                 520                 525

Ile Leu Trp Gln Glu Leu Leu Glu Glu Gln Cys Leu Leu Glu Ala Trp
    530                 535                 540

Leu Thr Glu Lys Glu Glu Ala Leu Asp Lys Val Gln Thr Ser Asn Phe
545                 550                 555                 560

Lys Asp Gln Lys Glu Leu Ser Val Ser Val Arg Arg Leu Ala Ile Leu
                565                 570                 575

Lys Glu Asp Met Glu Met Lys Arg Gln Thr Leu Asp Gln Leu Ser Glu
            580                 585                 590
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Ile Gly Gln Asp Val Gly Gln Leu Leu Ser Asn Pro Lys Ala Ser Lys
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Lys Met Asn Ser Asp Ser Glu Glu Leu Thr Gln Arg Trp Asp Ser Leu
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Val Gln Arg Leu Glu Asp Ser Ser Asn Gln Val Thr Gln Ala Val Ala
625                 630                 635                 640

Lys Leu Gly Met Ser Gln Ile Pro Gln Lys Asp Leu Leu Glu Thr Val
                645                 650                 655

His Val Arg Glu Gln Gly Met Val Lys Lys Pro Lys Gln Glu Leu Pro
            660                 665                 670

Pro Pro Pro Pro Pro Lys Lys Arg Gln Ile His Val Asp Leu Glu Lys
        675                 680                 685

Leu Arg Asp Leu Gln Gly Ala Met Asp Asp Leu Asp Ala Asp Met Lys
    690                 695                 700

Glu Val Glu Ala Val Arg Asn Gly Trp Lys Pro Val Gly Asp Leu Leu
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Ile Asp Ser Leu Gln Asp His Ile Glu Lys Thr Leu Ala Phe Arg Glu
                725                 730                 735

Glu Ile Ala Pro Ile Asn Leu Lys Val Lys Thr Met Asn Asp Leu Ser
            740                 745                 750

Ser Gln Leu Ser Pro Leu Asp Leu His Pro Ser Leu Lys Met Ser Arg
        755                 760                 765

Gln Leu Asp Asp Leu Asn Met Arg Trp Lys Leu Leu Gln Val Ser Val
    770                 775                 780

Asp Asp Arg Leu Lys Gln Leu Gln Glu Ala His Arg Asp Phe Gly Pro
785                 790                 795                 800

Ser Ser Gln His Phe Leu Ser Thr Ser Val Gln Leu Pro Trp Gln Arg
                805                 810                 815

Ser Ile Ser His Asn Lys Val Pro Tyr Tyr Ile Asn His Gln Thr Gln
            820                 825                 830

Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Phe Gln Ser Leu
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Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Ile Lys
    850                 855                 860

Ile Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Glu Leu Asn
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Thr Thr Asn Glu Val Phe Lys Gln His Lys Leu Asn Gln Asn Asp Gln
                885                 890                 895

Leu Leu Ser Val Pro Asp Val Ile Asn Cys Leu Thr Thr Thr Tyr Asp
            900                 905                 910

Gly Leu Glu Gln Leu His Lys Asp Leu Val Asn Val Pro Leu Cys Val
        915                 920                 925

Asp Met Cys Leu Asn Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr
    930                 935                 940

Gly Lys Ile Arg Val Gln Ser Leu Lys Ile Gly Leu Met Ser Leu Ser
945                 950                 955                 960

Lys Gly Leu Leu Glu Glu Lys Tyr Arg Cys Leu Phe Lys Glu Val Ala
                965                 970                 975

Gly Pro Thr Glu Met Cys Asp Gln Arg Gln Leu Gly Leu Leu Leu His
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Asp Ala Ile Gln Ile Pro Arg Gln  Leu Gly Glu Val Ala  Ala Phe Gly
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Gly Ser  Asn Ile Glu Pro Ser  Val Arg Ser Cys Phe  Gln Gln Asn
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Asn Asn  Lys Pro Glu Ile Ser  Val Lys Glu Phe Ile  Asp Trp Met
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His Leu  Glu Pro Gln Ser Met  Val Trp Leu Pro Val  Leu His Arg
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Val Ala  Ala Ala Glu Thr Ala  Lys His Gln Ala Lys  Cys Asn Ile
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Cys Lys  Glu Cys Pro Ile Val  Gly Phe Arg Tyr Arg  Ser Leu Lys
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His Phe  Asn Tyr Asp Val Cys  Gln Ser Cys Phe Phe  Ser Gly Arg
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Thr Ala  Lys Gly His Lys Leu  His Tyr Pro Met Val  Glu Tyr Cys
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Ile Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe Thr Lys Val
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Leu Lys Asn Lys Phe Arg Ser Lys Lys Tyr Phe Ala Lys His Pro
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Arg Leu Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn
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35 40 45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
50 55 60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65 70 75 80

Leu Arg Val Leu Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser Thr
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Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp Asn
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Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met Ala
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Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val Arg
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Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr Thr
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Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His Arg
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Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala Thr
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Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly Ile
195 200 205

Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp Lys
210 215 220

Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro Gln
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Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg Pro
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Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met His
260 265 270

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275 280 285

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Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln His
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Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ser Trp Leu Ser Glu
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Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp Gln
580 585 590

Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala Asp
595 600 605

Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys Gln
610 615 620

Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr Glu
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Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln Lys
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Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr Gln
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Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val Thr
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Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile Arg
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Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr Arg
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Ser Gly Leu Tyr Tyr Leu Ser Thr Thr Val Lys Glu Met Ser Lys Lys
        995                 1000                1005

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Asn His Ile Gln Thr Leu Lys Lys Trp Met Ala Glu Val Asp Val
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Phe Leu Lys Glu Glu Trp Pro Ala Leu Gly Asp Ser Glu Ile Leu
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Ser Leu Thr Phe Ile Asp Lys Gln Leu Ala Ala Tyr Ile Ala Asp
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Lys Val Asp Ala Ala Gln Met Pro Gln Glu Ala Gln Lys Ile Gln
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Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe Arg
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Leu Phe Gln Lys Pro Ala Asn Phe Glu Leu Arg Leu Gln Glu Ser
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Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu Glu
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Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn His
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Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu Val
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1835 1840 1845

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1865 1870 1875

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1940 1945 1950

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1955 1960 1965

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1985 1990 1995

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2015 2020 2025

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference UPN-Q3355PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/001768	International filing date *(day/month/year)* 21 January 2005 (21.01.2005)	Priority date *(day/month/year)* 23 January 2004 (23.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 24 July 2006 (24.07.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Dorothée Mülhausen e-mail: pt01@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
CATHY KODROFF
HOWSON AND HOWSON
SRPING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRINGS HOUSE, PA 19477

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference UPN-Q3355PCT	Date of mailing (*day/month/year*) 16 DEC 2005 FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/01768	21 January 2005 (21.01.2005)	23 January 2004 (23.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07K 1/00, 14/00; C07H 21/02, 21/04; A61K 31/70 and US Cl.: 530/350, 827; 53[illegible]23.1-23.5; 514/44

Applicant

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☒ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	07 November 2005 (07.11.2005)	Suzanne M. Mayer, Ph.D. Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/01768

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International appl
PCT/US05/01768

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9-15

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 9-15 are so unclear that no meaningful opinion could be formed *(specify)*:

The claims are dependent upon 'any of claims 1-8'. There is no claim 3 in the application thus no meaningful search of these claims can be made.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International appl
PCT/US05/01768

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 6	YES
	Claims 1,2,4,5,7-8 and 15-16	NO
Inventive step (IS)	Claims 6	YES
	Claims 1,2,4,5,7-8 and 15-16	NO
Industrial applicability (IA)	Claims 1,2,4-8 and 15-16	YES
	Claims 1,2,4-8 and 15-16	NO

2. Citations and explanations:

Claims 1,2,4,5, 7-8 and 16-17 lack novelty and inventive step under PCT Article 33(2) and 33(3) as being anticipated by TINSLEY et al. (US 6,518,413). Utrophin is a 3,433 amino acid protein with several different regions and domains and which is usually found in muscle tissues. Tinsley et al. teach a DNA molecule that is a utrophin "mini-gene" which expresses a polypeptide that encodes for a 2008 amino acid protein which possesses the N-terminal amino acid domain, and the C-terminal amino acid domain, but which is missing the majority of the central domain (approximately 1500 amino acids - attached amino acid sequence alignment of SEQ ID No: 5 and SEQ ID No: 8 of Tinsley et al.). The polynucleotide is clone is placed under the control of the human skeletal alpha-actin (HAS) promoter and regulatory regions (column 16, lines 55-62). This promoter is a muscle specific promoter. The DNA of the invention is used with adenovirus or retrovirus vectors (column 10, lines 1-3). Claim 2 is included in this rejection because the prior art suggests/teaches that utrophin only has two hinge regions. This is evidenced by van Deutekom et al. (Figure 1, p.776) and Winder et al.: "similarly utrophin is thought to contain 22 repeats and two hinges." (1st column, 1st line, p.28).

Claim 6 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest DNA that encodes a protein of SEQ ID Nos: 4, 2 and 5.

Claims 1-2, 4-8 and 16-17 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry. The microutrophin DNA and encoded proteins described in this application would be useful in the medical industry as a potential treatment supplement for muscle wasting diseases such as muscular dystrophy.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/01768

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The description is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof: The first page of the specification is missing.

The Brief Description of the Drawings section contains an error on p. 2, line 19. This line refers to Figures 3A-2K, it should refer to Figures 3A-3K.

Claims 1-17 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: There is no claim # 3 in the claim set. Thus the claims are incorrectly numbered after claim 2 and onwards.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US05/01768

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 2-8 and 16-17 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 2-8 and 16-17 are indefinite for the following reason(s): The independent claim is drawn to a DNA molecule. However, the inconsistent use of DNA terminology and protein (e.g. amino acid) terminology renders the claims indefinite. For example, in claim 6, the recitation of a nucleic acid according to claim 1, where the microutrophin is selected from the group having the amino acid sequence of SEQ ID No: 4. Correct claim construction in this circumstance dictates that the nucleic acid must encode for a protein having an amino acid sequence.

Claim 6 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 6 is indefinite for the following reason(s): Claim 6 recites a microutrophin selected from the group consisting of human, canine and mouse microutrophin having the amino acid sequences of SEQ ID Nos: 4, 2 and 5, respectively. However, "microutrophin" is not a naturally occurring protein. Instead the term is defined by Applicants themselves and it they are non-naturally occurring protein derived from human, canine and mouse, but not endogenous. Thus, claims a human microutrophin having the amino acid sequence of SEQ ID No: 4, for example, is wholly inaccurate and misleading.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
CATHY KODROFF
HOWSON AND HOWSON
SRPING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRINGS HOUSE, PA 19477

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	16 DEC 2005
Applicant's or agent's file reference UPN-Q3355PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/01768	21 January 2005 (21.01.2005)	23 January 2004 (23.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07K 1/00, 14/00; C07H 21/02, 21/04; A61K 31/70 and US Cl.: 530/350, 827; 53[illegible]23.1-23.5; 514/44

Applicant

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	07 November 2005 (07.11.2005)	Suzanne M. Mayer, Ph.D. Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/01768

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International appl
PCT/US05/01768

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9-15

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 9-15 are so unclear that no meaningful opinion could be formed *(specify)*:

The claims are dependent upon 'any of claims 1-8'. There is no claim 3 in the application thus no meaningful search of these claims can be made.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

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☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International appl
PCT/US05/01758

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 6	YES
	Claims 1,2,4,5,7-8 and 15-16	NO
Inventive step (IS)	Claims 6	YES
	Claims 1,2,4,5,7-8 and 15-16	NO
Industrial applicability (IA)	Claims 1,2,4-8 and 15-16	YES
	Claims 1,2,4-8 and 15-16	NO

2. Citations and explanations:

Claims 1,2,4,5, 7-8 and 16-17 lack novelty and inventive step under PCT Article 33(2) and 33(3) as being anticipated by TINSLEY et al. (US 6,518,413). Utrophin is a 3,433 amino acid protein with several different regions and domains and which is usually found in muscle tissues. Tinsley et al. teach a DNA molecule that is a utrophin "mini-gene" which expresses a polypeptide that encodes for a 2008 amino acid protein which possesses the N-terminal amino acid domain, and the C-terminal amino acid domain, but which is missing the majority of the central domain (approximately 1500 amino acids - attached amino acid sequence alignment of SEQ ID No: 5 and SEQ ID No: 8 of Tinsley et al.). The polynucleotide is clone is placed under the control of the human skeletal alpha-actin (HAS) promoter and regulatory regions (column 16, lines 55-62). This promoter is a muscle specific promoter. The DNA of the invention is used with adenovirus or retrovirus vectors (column 10, lines 1-3). Claim 2 is included in this rejection because the prior art suggests/teaches that utrophin only has two hinge regions. This is evidenced by van Deutekom et al. (Figure 1, p.776) and Winder et al.: "similarly utrophin is thought to contain 22 repeats and two hinges." (1st column, 1st line, p.28).

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/01768

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US05/01768

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Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/001768

International filing date: 21 January 2005 (21.01.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/538,877
Filing date: 23 January 2004 (23.01.2004)

Date of receipt at the International Bureau: 26 September 2005 (26.09.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

1369452

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 16, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/538,877*
FILING DATE: *January 23, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/01768*

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

16085 U.S. PTO

012304

PTO/SB/16 (10-01)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV222867963US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Hansell	STEDMAN	Philadelphia, PA
Leonard	SU	Philadelphia, PA
Marilyn	MITCHELL	Philadelphia, PA

☐ *Additional inventors are being named on the _____ separately numbered sheets attached hereto*

22264 U.S.PTO 60/538877 012304

TITLE OF THE INVENTION (500 characters max)

AAV MICROUTROPHIN AND METHODS OF USE THEREOF

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number — Type Customer Number here — Place Customer Number Bar Code Label here

OR

■ Firm *or* Individual Name	Lisa Burgin Conte, Esquire				
Address	Dilworth Paxson LLP				
Address	3200 Mellon Bank Center, 1735 Market Street				
City	Philadelphia	State	Pennsylvania	ZIP	19103
Country	US	Telephone	215.575.7356	Fax	215.575.7200

ENCLOSED APPLICATION PARTS (*check all that apply*)

■ Specification *Number of Pages* 5

■ Drawing(s) *Number of Sheets* 0

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify):

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

■ Applicant claims small entity status. See 37 CFR 1.27.

Filing Fee Amount ($): $80.00

■ A check of money order is enclosed to cover the filing fees

☑ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account No. 50-0979.

☐ Payment by credit card. Form PTO-2038 is attached.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

■ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Lisa Burgin Conte

Lisa Burgin Conte, Reg. No. 52,470

Date: January 23, 2004

Attorney Docket No. Q3355

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

EV222867963US

526166_1

AAV MICROUTROPHIN AND METHODS OF USE THEREOF

Description of the Technology:

This document discloses the construction and intended use of a microutrophin coding sequence in the treatment of the most common X-linked lethal disease in man. The goal is to use this new construction in the context of recombinant AAV delivered to skeletal and ultimately cardiac muscle as outlined in previous technology disclosures.

Duchenne Muscular Dystrophy (DMD) is caused by a deficiency of the muscle cytoskeletal protein known as dystrophin(Hoffman, Brown et al. 1987; Hoffman, Fischbeck et al. 1988). Dystrophin is a member of the spectrin superfamily of proteins and as such is distantly related to spectrin and alpha-actinin(Koenig, Monaco et al. 1988). Dystrophin is most closely related to the protein utrophin(Tinsley, Blake et al. 1992). The genes for these two proteins have nearly identical intron/exon structures, and the proteins are 50+% homologous at the amino acid level. Dystrophin is expressed throughout the entire length of the skeletal muscle fiber while utrophin is normally expressed only at the neuromuscular junction. Most cases of DMD result from sporadic deletions of the X chromosomal dystrophin gene(Koenig, Beggs et al. 1989). The destruction of the dystrophin open reading frame by these mutations suggests that therapies that genetically reconstitute dystrophin expression will elicit a cellular immune response against the fibers in which the protein is synthesized.

In the years following the initial discovery of utrophin, the technologies for targeted gene ablation in mice facilitated a formal genetic analysis of gene complementation. In the transgenic mouse in which the expression of utrophin is dictated by a muscle-specific promoter, utrophin can complement the physiological role of dystrophin(Tinsley, Potter et al. 1996; Tinsley, Deconinck et al. 1998). This has prompted a multi-million dollar reasearch effort to find pharmacological means of upregulating the expression of utrophin in the muscle of patients with DMD(Burton, Tinsley et al. 1999; Perkins, Burton et al. 2001).

Our strategy is different: somatic transfer of a micro-utrophin encoding DNA sequence under the control of a muscle-specific promoter(Stedman 2001). Recently published studies from several groups have demonstrated the utility of AAV-sized microdystrophin cassettes for reversing the pathology of dystrophin deficiency in

mice(Wang, Li et al. 2000; Harper, Hauser et al. 2002). Building on this advance, we have constructed a microutrophin cassette for use in probing both the functional restoration of dystrophin and the immune response. Our preferred animal model for these studies is the German Short Haired Pointer dog, because of its complete deletion of the dystrophin coding sequence(Schatzberg, Olby et al. 1999). All other "dystrophin-deficient" animal models described to date derive from point mutations, with the end result that the immune systems in these animals are predicted to develop tolerance to the peptide encoded by the remainder of the dystrophin open reading frame(Schatzberg, Anderson et al. 1998; Lu, Morris et al. 2000). In the GSHP dog model we will be able to study in detail the immune response to recombinant canine dystrophin and utrophin, when these proteins are produced from somatically delivered AAV vectors. On completion of these studies we will have answered essential questions about the relative safety and efficacy of the two methods for treating DMD by somatic gene transfer.

Sequence 1
Microutrophin Nucleotide Sequence

ATCGATCCACCATGGCCAAGTATGGAGAACATGAAGCCAGTCCTGATAATGGGCAGAACGAATTCAGTGACATCATTAA
GTCCAGATCTGATGAACACAATGACGTGCAGAAGAAAACCTTTACCAAATGGATCAATGCGCGATTTTCAAAGAGTGGA
AAACCACCCATCAATGATATGTTCACAGACCTCAAAGATGGAAGGAAGCTCCTGGATCTTCTGGAAGGCCTCACAGGAA
CATCACTGCCAAAGGAACGTGGTTCCACAAGGGTACATGCTTTAAATAATGTCAACAGAGTGCTGCAGGTTTTGCATCA
GAATAATGTGGATTTAGTGAATATAGGAGGAACTGACATTGTAGATGGAAATCACAAACTGACTTTGGGATTACTTTGG
AGCATCATTTTGCACTGGCAGGTAAAAGATGTCATGAAAGATGTCATGTCAGACCTGCAGCAGACAAACAGTGAGAAGA
TCCTACTGAGCTGGGTGCGCCAGTCTACTAGGCCGTACAGCCAGGTCAACGTCCTCAACTTCACCACCAGCTGGACAGA
TGGACTGGCCTTTAATGCTGTGCTGCACCGACATAAACCTGATCTCTTCAGCTGGGATAGAGTTGTCAAAATGTCCCCA
ATTGAGAGACTTGAACATGCCTTCAGCAAAGCTCAAACTTATTTGGGAATTGAAAAGCTGTTAGATCCTGAAGATGTTG
CCGTTCAACTTCCTGACAAGAAATCCATAATTATGTATTTAACATCTTTGTTTGAGGTGCTTCCTCAGCAAGTCACTCT
AGATGCCATCCGTGAAGTAGAGACACTCCCAAGGAAATATAAGAAAGAATGTGAAGAAGGAGAGATTAGTATACAGAGC
TCAGCGCCAGAGGAGGAGCATGAGTGTCCCGGAGCTGAAACCCCCAGCACTGTCACTGAAGTTGACACGGATCTGGACA
GCTATCAGATAGCACTGGAGGAAGTGCTGACCTGGTTGCTTTCTGCCGAGGACACTTTCCAGGAGCAGGATGACATTTC
TGATGATGTAGAAGAAGTCAAAGAGCAGTTTACTACCCATGAAGCTTTTATGATGGAGCTGACAGCGCACCAGAGCAGT
GTGGGCAGTGTCCTGCAGGCAGGAAACCAGCTGATAACGCAAGGAACTCTGTCAGATGAGGAGGAATTTGAAATTCAGG
AACAAATGACCCTGCTAAATGCTAGATGGGAGGCACTCAGGGTGGATAGTATGAACAGACAGTCCCGGCTGCATGATGT
GTTGATGGAACTACAAAAGAAGCAGTTGCAACAGCTCTCTGCCTGGTTAACACTCACAGAAGAACGCATTCAGAAGATG
GAAACCTGCCCCCTGGATGATGATTTAAAATCCCTACAAAAGCTACTAGAAGATCATAAACGTTTGCAAAATGATCTTG
AGGCGGAACAGGTGAAGGTAAATTCACTAACACACATGGTGGTGATTGTTGATGAAAACAGTGGTGAGAGTGCCACTGC
TGTTCTGGAAGATCAGTTACAGAAACTTGGTGAACGCTGGACAGCAGTGTGCCGTTGGACAGAGGAACGTTGGAGTAGG
CTACAAGAAATTAATATATTGTGGCAGGAATTATTAGAAGAACAGTGCTTGTTGAAAGCTTGGCTAACTGAAAAAGAAG
AGGCCTTAAATAAAGTCCAGACGAGCAACTTCAAAGACCAAAAGGAACTAAGTGTCAGCATCCGACGATTGGCTATTTT
GAAGGAAGACATGGAAATGAAACGTCAGGCATTGGATCAGCTAAGTGAGATTGGCCAGGATGTGGGTCAATTAGTTGAT
AATCCCAAGGCATCTAAGAAGATCAACAGTGACTCAGAGGAACTAACTCAGAGATGGGATTCTTTGGTTCAGAGACTAG
AAGATTCCTCTAACCAGGTGACTCAGGCTGTGGCAAAGCTGGGGATGTCCCAAATTCCTCAGAAAGATCTTCTGGAGAC
TGTTCGCATAAGAGAACAAGTAACTACAAAAAGGTCTAAGCAAGAACTGCCTCCTCCTCCTCCCCCAAAGAAGAGACAG
ATTCCTGTCGACCTGGAGAAGCTCAGAGACCTGCAGGGAGCCATGGATGACCTGGATGTTGACATGAAGGAGGCGGAGG
CTGTGAGGAATGGCTGGAAGCCTGTGGGAGACTTACTTATCGACTCACTGCAGGATCACATTGAAAAAACCATGGCATT
TAGAGAAGAAATTGCACCAATCAACCTAAAAGTTAAAACAGTGAATGATTTATCCAGTCAGCTGTCTCCACTTGACCTG
CATCCATCTCTAAAGATGTCTCGCCAGCTAGATGACCTTAATATGCGATGGAAACTTCTGCAGGTTTCTGTGGATGATC
GCCTTAAACAGCTTCAGGAAGCCCATAGAGATTTTGGGCCATCCTCTCAGCATTTTCTTTCTACTTCAGTCCAGCTGCC
ATGGCAAAGATCCATTTCACATAATAAAGTGCCCTATTACATCAACCATCAAACACAGACAACTTGTTGGGACCGTCCT
AAAATGACTGAACTCTTTCAATCTCTTGCTGACCTGAATAATGTACGTTTCTCTGCCTACCGTACAGCCATCAAAATCC
GAAGACTACAAAAAGCACTGTGTTTGGATCTCTTAGAGTTGAATACAACAAATGAAGTTTTCAAGCAGCACAAACTGAA
CCAAAATGATCAGCTTCTTAGCGTTCCAGATGTCATCAACTGTCTGACAACAACTTATGATGGTCTTGAACAAATGCAT
AAGGATCTGGTCAACGTTCCACTCTGTGTGGATATGTGTCTCAACTGGTTGCTCAATGTGTATGACACGGGTCGAACTG
GAAAAATAAGAGTGCAGAGTCTGAAGATTGGATTGATGTCTCTCTCCAAAGGTCTCTTAGAAGAAAAATACAGATATCT
CTTTAAGGAGGTGGCAGGTCCGACAGAAATGTGTGACCAGAGGCAGCTTGGCCTGTTACTTCATGATGCCATCCAGATC
CCTCGGCAGCTGGGGGAAGTAGCAGCTTTTGGGGGCAGTAATATTGAACCCAGTGTTCGCAGCTGCTTCCAACAGAATA
ACAATAAGCCAGAGATAAGCGTAAAAGATTTTATAGATTGGATGCGTCTGGAACCACAGTCCATGGTTTGGCTGCCAGT
TTTACACCGAGTGGCTGCAGCTGAGACTGCAAAGCATCAAGCTAAATGCAACATCTGTAAAGAATGTCCAATAGTTGGG
TTCAGGTATAGAAGCCTAAAGCATTTTAACTATGATGTCTGCCAGAGTTGCTTTTTTTCGGGTCGAACGGCAAAAGGTC
ACAAATTACATTACCCAATGGTGGAATATTGTATACCTACAACATCTGGGGAAGATGTACGAGACTTCACAAAGGTGCT
GAAGAATAAGTTCAGATCAAAGAAATACTTTGCCAAACATCCTCGGCTTGGCTACCTGCCTGTCCAGACAGTACTTGAA
GGTGACAACTTAGAGACTTGAAAAACTCGAG

Sequence 2
Microutrophin Peptide Sequence

MAKYGEHEASPDNGQNEFSDIIKSRSDEHNDVQKKTFTKWINARFSKSGKPPINDMFTDL
KDGRKLLDLLEGLTGTSLPKERGSTRVHALNNVNRVLQVLHQNNVDLVNIGGTDIVDGNH
KLTLGLLWSIILHWQVKDVMKDVMSDLQQTNSEKILLSWVRQSTRPYSQVNVLNFTTSWT
DGLAFNAVLHRHKPDLFSWDRVVKMSPIERLEHAFSKAQTYLGIEKLLDPEDVAVQLPDK
KSIIMYLTSLFEVLPQQVTLDAIREVETLPRKYKKECEEGEISIQSSAPEEEHECPGAET
PSTVTEVDTDLDSYQIALEEVLTWLLSAEDTFQEQDDISDDVEEVKEQFTTHEAFMMELT
AHQSSVGSVLQAGNQLITQGTLSDEEEFEIQEQMTLLNARWEALRVDSMNRQSRLHDVLM
ELQKKQLQQLSAWLTLTEERIQKMETCPLDDDLKSLQKLLEDHKRLQNDLEAEQVKVNSL
THMVVIVDENSGESATAVLEDQLQKLGERWTAVCRWTEERWSRLQEINILWQELLEEQCL
LKAWLTEKEEALNKVQTSNFKDQKELSVSIRRLAILKEDMEMKRQALDQLSEIGQDVGQL
VDNPKASKKINSDSEELTQRWDSLVQRLEDSSNQVTQAVAKLGMSQIPQKDLLETVRIRE
QVTTKRSKQELPPPPPPKKRQIPVDLEKLRDLQGAMDDLDVDMKEAEAVRNGWKPVGDLL
IDSLQDHIEKTMAFREEIAPINLKVKTVNDLSSQLSPLDLHPSLKMSRQLDDLNMRWKLL
QVSVDDRLKQLQEAHRDFGPSSQHFLSTSVQLPWQRSISHNKVPYYINHQTQTTCWDRPK
MTELFQSLADLNNVRFSAYRTAIKIRRLQKALCLDLLELNITTNEVFKQHKLNQNDQLLSV
PDVINCLTTTYDGLEQMHKDLVNVPLCVDMCLNWLLNVYDTGRTGKIRVQSLKIGLMSLS
KGLLEEKYRYLFKEVAGPTEMCDQRQLGLLLHDAIQIPRQLGEVAAFGGSNIEPSVRSCF
QQNNNKPEISVKDFIDWMRLEPQSMVWLPVLHRVAAAETAKHQAKCNICKECPIVGFRYR
SLKHFNYDVCQSCFFSGRTAKGHKLHYPMVEYCIPTTSGEDVRDFTKVLKNKFRSKKYFA
KHPRLGYLPVQTVLEGDNLET

We Claim:

1. A microutrophin cassette for treatment of Duchenne Muscular Dystrophy (DMD) by somatic gene transfer.

2. A method of using the microutrophin cassette of claim 1 for restoration of dystrophin.

3. A method of using the microutrophin cassette of claim 1 to generate an immune response.

4. A method of treating dystrophin deficiency by somatic gene transfer.

5. The nucleotide sequence embodied in sequence 1 that encodes a microutrophin molecule, wherein the microutrophin molecule is homologous to the human dystrophin homolog utrophin.

6. A microutrophin molecule embodied in the polypeptide sequence of sequence 2, wherein the microutrophin molecule is homologous to the human dystrophin protein homolog utrophin.

7. A method of treatment using the nucleotide sequence of claim 5 wherein the nucleotide sequence is delivered to human cells by one or more gene vectors from the group comprising adenovirus, adeno associated virus, lentivirus and plasmids.

8. A method of using the sequence of claim 5 in gene therapy applications to treat muscle disorders.

9. A method of using the sequence of claim 5 in gene therapy applications to treat muscular dystrophy.

10. A method of using the sequence of claim 5 in gene therapy applications to treat Duchenne Muscular Dystrophy.

11. A method of using the microutrophin molecule of claim 6 to treat muscle disorders.

12. A method of using the microutrophin molecule of claim 6 to treat muscular dystrophy.

13. A method of using the microutrophin molecule of claim 6 to treat Duchenne Muscular Dystrophy.

14. A nucleotide sequence that is at least 50% homologous to the nucleotide sequence of claim 5.

15. A polypeptide sequence that is at least 50% homologous to the polypeptide sequence of claim 6.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
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(PCT Administrative Instructions, Section 411)

To:

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Date of mailing *(day/month/year)* 27 October 2005 (27.10.2005)	
Applicant's or agent's file reference UPN-Q3355PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US2005/001768	International filing date *(day/month/year)* 21 January 2005 (21.01.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 23 January 2004 (23.01.2004)
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* **An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 January 2004 (23.01.2004)	60/538,877	US	26 September 2005 (26.09.2005)

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